Mary 2001

Access DB# 21942

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Phyllis Spivack Examiner #: 70400 Date: 8/1/00
Art Unit: 1614 Phone Number 30 84703 Serial Number: 09/529,050
Mail Box and Bldg/Room Location: 2D05 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, ~~keywords, synonyms,~~ acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Medicaments

Inventors (please provide full names): Allen Wayne Mangel
Allison Ruth Northcutt

Earliest Priority Filing Date: ~~10/5/98~~ 10/7/97

***For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.**

C6.405.469.158.272
Please search methods for the treatment of irritable bowel syndrome (IBS) colonic diseases, functional / intestinal disease
C6.405.469.237 C23.888.821.214
characterized by - diarrhea - predominant
C6.405.469.187
- alternating constipation/diarrhea
C23.888.821.150
- no constipation
antidiarrhea? rehydrat? solu. defecat? feces

1505
1438-48

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

comprising administering a 5-HT_3 receptor antagonist selected from alosetron, granisetron, azasetron, tropisetron, ramosetron, ondansetron, lerisetron, zacopride, cilansetron, itasetron, indisetron, dolasetron.....thank

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher: [redacted]	NA Sequence (#)	STN
Searcher Phone #: 0	AA Sequence (#)	Dialog
Searcher Location:	Structure (#)	Questel/Orbit
Date Searcher Picked Up: 8/3	Bibliographic	Dr.Link
Date Completed:	Litigation	Lexis/Nexis
Searcher Prep & Review Time: 7	Fulltext	Sequence Systems
Clerical Prep Time:	Patent Family	WWW/Internet
Online Time: 27	Other	Other (specify)

PTO-1590 (1-2000)

Spivack
529050

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=> fil reg

COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       1.20       1.20

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=> e "5-ht3 receptor antagonist"/cn 5

E1            1     5-HT3 RECEPTOR (MOUSE CLONE .LAMBDA.2141 SHORT FORM)/CN
E2            1     5-HT3 RECEPTOR (RABBIT STRAIN DUTCH-BELTED FRAGMENT)/CN
E3            0 --> 5-HT3 RECEPTOR ANTAGONIST/CN
E4            1     5-HT3A RECEPTOR (HUMAN CLONE H5-HT3RL (LONG ISOFORM))/CN
E5            1     5-HT3A RECEPTOR (HUMAN CLONE H5HT3K2)/CN

=> s (alosetron or granisetron or azasetron or tropisetron or ramosetron or
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indisetron or dolasetron)/cn

             1 ALOSETRON/CN
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             1 TROPISETRON/CN
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             1 ONDANSETRON/CN
             1 LERISETRON/CN
             1 ZACOPRIDE/CN
             0 CLIANSETRON/CN   dansetron
             1 ITASETRON/CN
             1 INDISETRON/CN
             1 DOLASETRON/CN
L1          11 (ALOSETRON OR GRANISETRON OR AZASETRON OR TROPISETRON OR
RAMOSET
               RON OR ONDANSETRON OR LERISETRON OR ZACOPRIDE OR CLIANSETRON
OR
               ITASETRON OR INDISETRON OR DOLASETRON)/CN

=> fil medl,caplus,biosis,embase,wpids

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=> s (alosetron or granisetron or azasetron or tropisetron or ramosetron or ondansetron or lerisetron or zacopride or cliansetron or itasetron or indisetron or dolasetron or l1) and (c6.405.469.158.272/ct or c6.405.469.237/ct or c6.405.469.187/ct or c23.888.8

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L2 3026 FILE MEDLINE
L3 2176 FILE CAPLUS
L4 3090 FILE BIOSIS
L5 5918 FILE EMBASE
L6 76 FILE WPIDS

TOTAL FOR ALL FILES
L7 14286 (ALOSETRON OR GRANISETRON OR AZASETRON OR TROPISETRON OR RAMOSET
RON OR ONDANSETRON OR LERISETRON OR ZACOPRIDE OR CLIANSETRON OR
ITASETRON OR INDISETRON OR DOLASETRON OR L1)

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L8 256 FILE MEDLINE
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L10 242 FILE MEDLINE
L11 117 FILE CAPLUS
L12 199 FILE BIOSIS
L13 719 FILE EMBASE
L14 17 FILE WPIDS

TOTAL FOR ALL FILES
L15 1294 (L7 OR 5 HT3 RECEPTOR ANTAGONIST) AND (C6.405.469.237/CT OR C6.405.469.187/CT OR C23.888.821.150/CT OR C23.888.821.214/CT OR ?DIARRH? OR REHYDRAT? SOLUT? OR DEFECAT? OR FECES OR CONSTIPA
T?)

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L16 25 FILE MEDLINE
L17 23 FILE CAPLUS
L18 24 FILE BIOSIS
L19 50 FILE EMBASE
L20 11 FILE WPIDS

TOTAL FOR ALL FILES
L21 133 L15 AND (IBS OR IRRITABLE BOWEL SYNDROME OR C6.405.469.158.272/C
T OR COLONIC DISEASE(2A) FUNTIONAL OR INTESTIN? DISEASE)

=> s l21 and (therap? or treat?)

L22 21 FILE MEDLINE
L23 17 FILE CAPLUS
L24 14 FILE BIOSIS
L25 47 FILE EMBASE
L26 11 FILE WPIDS

TOTAL FOR ALL FILES
L27 110 L21 AND (THERAP? OR TREAT?)

=> dup rem l27

PROCESSING COMPLETED FOR L27
L28 69 DUP REM L27 (41 DUPLICATES REMOVED)

=> d cbib abs 1-69;s mangel a?/au,in;s northoutt a?/au,in

L28 ANSWER 1 OF 69 MEDLINE DUPLICATE 1
2000205955 Document Number: 20205955. Efficacy and safety of **alosetron** in women with **irritable bowel syndrome**: a randomised, placebo-controlled trial [see comments].
Camilleri M; Northcutt A R; Kong S; Dukes G E; McSorley D; Mangel A W.
(Gastrointestinal Research Unit, Mayo Clinic, Rochester, MN, USA.)

LANCET, (2000 Mar 25) 355 (9209) 1035-40. Journal code: L0S. ISSN: 0140-6736. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: **Irritable bowel syndrome** (**IBS**) is a common gastrointestinal disorder with symptoms of abdominal pain, discomfort, and altered bowel function. Antagonists of the type 3 serotonin receptor (5-HT3) have shown promising results in the relief of **IBS**-associated symptoms. We aimed to confirm these findings by doing a randomised, placebo-controlled trial. METHODS: We studied 647 female **IBS** patients with **diarrhoea** -predominant or alternating bowel patterns (**diarrhoea** and **constipation**). 324 patients were assigned 1 mg **alosetron** and 323 placebo orally twice daily for 12 weeks, followed by a 4-week post-**treatment** period. Adequate relief of abdominal pain and discomfort was the primary endpoint; secondary endpoints included improvements in urgency, stool frequency, and stool consistency. Analysis was by intention to **treat**. FINDINGS: 79 (24%) of patients in the **alosetron** group and 53 (16%) in the placebo group dropped out. The difference in the drop-out rate between groups was mainly due to a greater occurrence of **constipation** in the **alosetron** group. A greater proportion of **alosetron-treated** patients than placebo-**treated** patients (133 [41%] vs 94 [29%], respectively) reported adequate relief for all 3 months of **treatment** (difference 12% [4.7-19.2]). **Alosetron** also significantly decreased urgency and stool frequency, and increased stool firmness. **Constipation** occurred in 30% and 3% of patients in the **alosetron** and placebo groups, respectively. INTERPRETATION: **Alosetron** was well tolerated and clinically effective in alleviating pain and bowel-related symptoms in this population of women with **IBS**.

L28 ANSWER 2 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

2000244735 EMBASE Effects of **alosetron** on gastrointestinal transit time and rectal sensation in patients with **irritable bowel syndrome**. Thumshirn M.; Coulie B.; Camilleri M.; Zinsmeister A.R.; Burton D.D.; Van Dyke C.. Dr. M. Camilleri, Mayo Clinic, Gastroenterology Research Unit, 200 First St. S.W., Rochester, MN 55905, United States. Alimentary Pharmacology and Therapeutics 14/7 (869-878) 2000.

Refs: 51.

ISSN: 0269-2813. CODEN: APTHEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Background: **Alosetron**, a **5-HT3-receptor antagonist**, relieves abdominal pain and improves bowel function in non-**constipated**, female patients with **irritable bowel syndrome**. 5-HT3 antagonists delay colonic transit, increase colonic compliance, and increase small intestinal water absorption. Aim: To evaluate the effects of **alosetron** on gastrointestinal and colonic transit, rectal compliance and rectal sensation in **irritable bowel syndrome**. Methods: A double-blind, placebo-controlled, two-dose study of **alosetron** was performed in 25 non-**constipated** **irritable bowel syndrome** patients, with paired studies before and after 4 weeks of **treatment** with placebo (n =

5), 1 mg **alosetron** (n = 10) or 4 mg (n = 10) **alosetron** b.d. Gastrointestinal and colonic transit were measured by scintigraphy. Rectal compliance and sensation were assessed by rectal balloon distention with a barostat. Results: There was a trend (P = 0.06) for 1 mg **alosetron** to increase rectal compliance (median pressure at half maximum volume 11 mmHg after **alosetron** vs. 15.6 mmHg before **alosetron**). The 1 mg b.d. **alosetron** dose non-significantly retarded proximal colonic transit. **Alosetron** and placebo reduced sensory scores relative to baseline values; none of the changes induced by **alosetron** was significant relative to placebo. Conclusions: **Alosetron** had no significant effect on gastrointestinal transit or rectal sensory and motor mechanisms in non-**constipated irritable bowel syndrome** patients in this study. **Alosetron**'s effects on colonic sensorimotor function and central sensory mechanisms deserve further evaluation.

L28 ANSWER 3 OF 69 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 2
2000:510666 **Alosetron**, a **5-HT3 receptor antagonist**, delays colonic transit in patients with **irritable bowel syndrome** and healthy volunteers. Houghton, L. A.; Foster, J. M.; Whorwell, P. J. (Department of Medicine, University Hospital of South Manchester, Manchester, M20 2LR, UK). Aliment. Pharmacol. Ther., 14(6), 775-782 (English) 2000. CODEN: APTHEN. ISSN: 0269-2813. Publisher: Blackwell Science Ltd..

AB **Alosetron** is a potent and selective **5-HT3 receptor antagonist**, which has been shown to be beneficial in the **treatment** of female patients with non-**constipated irritable bowel syndrome**. To investigate the effect of **alosetron** on whole gut, small bowel and colonic transit in patients with **irritable bowel syndrome** (Study 1) and healthy volunteers (Study 2). Thirteen patients with **irritable bowel syndrome** and 12 healthy volunteers. Both studies were randomized, double-blind, placebo-controlled with a two-way crossover design, in which each subject received **alosetron** (2 mg b.d. administered orally) or placebo for 8 days. Mean whole gut transit was detd. from the excretion of radio-opaque markers; small bowel transit was detd. from rise in breath hydrogen after a meal; and colonic transit and segmental transit were evaluated from abdominal X-ray. In addn., colonic transit was calcd. by subtracting small bowel transit time from whole gut transit time. **Alosetron** increased colonic transit time by prolonging left colonic transit in both patients with **irritable bowel syndrome** and controls. This resulted in a tendency for the whole gut transit to be delayed in **irritable bowel syndrome** patients (P = 0.128), which was confirmed in controls (P = 0.047). **Alosetron** delays colonic transit by prolonging left colonic transit. These results add to the body of evidence suggesting that **alosetron** should have a **therapeutic** role in patients with non-**constipated irritable bowel**

syndrome.

L28 ANSWER 4 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000158546 EMBASE Review article: New insights into the pathogenesis of radiation-induced intestinal dysfunction. MacNaughton W.K.. Dr. W.K. MacNaughton, Department Physiology Biophysics, University of Calgary, 3330
Hospital Dr. NW, Calgary, Alta. T2N 4N1, Canada. wmacnaug@ucalgary.ca.
Alimentary Pharmacology and Therapeutics 14/5 (523-528) 2000.
Refs: 51.
ISSN: 0269-2813. CODEN: APTHEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Exposure of the abdomino-pelvic region to ionizing radiation, such as that
received during radiotherapy, is associated with the development of a number of untoward symptoms which may limit the course of **therapy** or which may involve serious chronic **intestinal disease**. While the mucosal dysfunction surrounding acute radiation enteritis is generally ascribed to the effects of ionizing radiation on the cell cycle of epithelial stem cells of the intestinal crypts and subsequent epithelial loss, recent evidence suggests that other, earlier events also play a role. The severity of these early events may determine the incidence and severity of chronic enteritis. The mechanism for this is unclear, but may relate to radiation-induced compromise of host defence responses to luminal pathogens or antigens. This review will address the current state of knowledge of the pathogenesis of radiation-induced intestinal dysfunction, focusing on events which occur in the mucosa, and will discuss what the future may hold with respect to the **treatment** of radiation-associated diseases of the intestinal tract.

L28 ANSWER 5 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000203693 EMBASE **Alosetron** approved for **treatment** of **irritable bowel syndrome**. American Journal of Health-System Pharmacy 57/6 (519) 15 Mar 2000.
ISSN: 1079-2082. CODEN: AHSPEK. Pub. Country: United States. Language: English.

L28 ANSWER 6 OF 69 MEDLINE DUPLICATE 3
2000236591 Document Number: 20236591. **Alosetron**. Balfour J A; Goa K L; Perry C M. (Adis International Limited, Mairangi Bay, Auckland, New Zealand.) DRUGS, (2000 Mar) 59 (3) 511-8; discussion 519-20. Ref: 39.
Journal code: EC2. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.
AB **Alosetron** is a potent and highly selective serotonin **5-HT3 receptor antagonist** which has been evaluated for the management of **irritable bowel syndrome** (**IBS**). It blocked the fast 5HT3-mediated depolarisation of guinea-pig myenteric and submucosal neurons in vitro, with half-maximal inhibition at approximately 55 nmol/L. **Alosetron** attenuated the visceral nociceptive effect of rectal distension in conscious or anaesthetised dogs. It increased the compliance of the colon to distension in patients with **IBS** and delayed colonic transit in patients with **IBS** or carcinoid **diarrhoea** and in healthy volunteers. A single dose of **alosetron** 4 mg increased in vivo fluid absorption in normal human small intestine. In clinical trials

in patients with **IBS**, **alosetron** 1 mg twice daily was effective in relieving abdominal pain and discomfort. **Alosetron** was most effective in female patients and particularly in those with **diarrhoea**-predominant **IBS**. In patients with **IBS** and healthy volunteers who received **alosetron**, the most common adverse event was **constipation**.

L28 ANSWER 7 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000134581 EMBASE **Alosetron** found to be effective for **IBS**
. Pharmaceutical Journal 264/7090 (504) 1 Apr 2000.
ISSN: 0031-6873. CODEN: PHJOAV. Pub. Country: United Kingdom. Language: English.

L28 ANSWER 8 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000187823 EMBASE **Alosetron**: A **5-HT3 receptor antagonist** for **treatment** of **irritable bowel syndrome**. Reddy P.. Dr. P. Reddy, Department of Pharmacy Practice, Univ. of Connecticut Sch. of Pharm., Storrs, CT, United States. Formulary 35/5 (404-411) 2000.
Refs: 21.
ISSN: 1082-801X. CODEN: FORMF. Pub. Country: United States. Language: English. Summary Language: English.
AB **Alosetron** is a **5-HT3 receptor antagonist** recently approved for the **treatment** of **diarrhea**-predominant **irritable bowel syndrome** (**IBS**) in women. Early studies in both men and women with **IBS** found **alosetron** to have preferential efficacy in women. In two 12-week phase III trials, women who received **alosetron** 1 mg twice daily were significantly more likely to respond to **therapy** than were women who received placebo. Moreover, significantly more **alosetron** recipients experienced reductions in stool frequency and urgency and improvements in stool consistency. Response was typically seen within 1 to 4 weeks of initiating **therapy**. **Constipation** was the only adverse effect reported significantly more often with **alosetron** than with placebo (28% vs 5% incidence). **Alosetron** appears to be effective in the management of **diarrhea**- predominant **IBS** and represents a new **therapeutic** modality for the management of this disease.

L28 ANSWER 9 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000240466 EMBASE **Alosetron** in **irritable bowel syndrome** (multiple letters). McColl K.E.L.; Mangel A.W.. K.E.L. McColl, Department of Medicine Therapeutics, Gardiner Institute, Western Infirmary, Glasgow G11 6NT, United Kingdom.
K.E.L.McColl@clinmed.gla.ac.uk
. Lancet 356/9224 (164-165) 8 Jul 2000.
Refs: 0.
ISSN: 0140-6736. CODEN: LANCAO. Pub. Country: United Kingdom. Language: English.

L28 ANSWER 10 OF 69 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 4
2000:16649 Document No. 132:175203 Pharmacology and clinical experience with **alosetron**. Camilleri, Michael (Gastroenterology Research Unit,

Mayo Clinic and Mayo Foundation, Rochester, MN, 55905, USA). Expert Opin.
Invest. Drugs, 9(1), 147-159 (English) 2000. CODEN: EOIDER. ISSN: 1354-3784. Publisher: Ashley Publications.

AB A review with 27 refs. **Alosetron** (Lotronex) is a potent, highly selective 5-HT3 antagonist. Animal models have shown it to be active in anxiety, psychosis, cognitive impairment, emesis and drug withdrawal, though its application in humans has been almost entirely restricted to **irritable bowel syndrome** (**IBS**).
Alosetron does not cause adverse pharmacodynamic effects, is absorbed rapidly after oral administration and is widely distributed throughout tissues after oral or iv. dosing in animals. Its metab. is rapid and extensive with N-demethylation, hydroxylation and oxidn. The drug, or its two principal metabolites, is equally excreted through the biliary tract and kidneys. **Alosetron** has proved safe in a range of toxicity studies; at high repeated dosing, clin. signs were transient and repeated administration produced no significant adverse effects on fertility, reproductive performance or fetal development. In pharmacokinetic studies, bioavailability of **alosetron** in healthy volunteers is approx. 60% and the plasma half-life is about 1.5 h. There are some gender differences in the pharmacokinetic profile, with 30-50% higher **alosetron** concns. in females. No consistent differences in **alosetron** serum concns. between the young and elderly were obsd. The pharmacokinetics of single, oral doses of **alosetron** are linear up to 8 mg. In human pharmacodynamic studies, **alosetron** increased basal jejunal water and electrolyte absorption, increased colonic transit time and, consequently, whole gut transit time. **Alosetron** has been evaluated in two large Phase II trials (randomized, double-blinded, placebo-controlled) and in Phase III trials which included a four-week observation period after cessation. Dose response studies suggested that the effective dosages could be between 1 and 2 mg, twice-daily. In Phase II trials, **alosetron**, 1 mg b.i.d., resulted in a greater proportion of non-**constipated** **IBS** patients reporting adequate relief of pain and discomfort, as well as improvement of bowel symptoms, frequency, urgency and stool consistency when compared with placebo. However, this beneficial effect was seen exclusively among females. Phase III studies evaluated exclusively females with non-**constipated** **IBS** and confirmed the results of the Phase II studies. **Alosetron** was well-tolerated in all studies, with the most frequently recorded adverse event being **constipation**. Thus, **alosetron** appears promising in the **treatment** of abdominal pain and discomfort and normalizing of bowel function in patients with non-**constipated** **IBS**. It also improves quality of life, has a high degree of tolerability and has an excellent safety profile to date.

L28 ANSWER 11 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000244082 EMBASE **Alosetron** (Lotronex) for **treatment** of **irritable bowel syndrome**. Medical Letter on Drugs and Therapeutics 42/1081 (53-54) 26 Jun 2000.
ISSN: 0025-732X. CODEN: MELEAP. Pub. Country: United States. Language: English.

L28 ANSWER 12 OF 69 MEDLINE DUPLICATE 5
2000098333 Document Number: 20098333. A double-blind, randomized, placebo-controlled dose-ranging study to evaluate the efficacy of

alosetron in the **treatment** of **irritable bowel syndrome**. Bardhan K D; Bodemar G; Geldof H; Schutz E; Heath A; Mills J G; Jacques L A. (Rotherham General Hospital, UK.) ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (2000 Jan) 14 (1) 23-34. Journal code: A5D. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB BACKGROUND: **Irritable bowel syndrome** is a common gastrointestinal disorder characterized by abdominal pain and discomfort and altered bowel habit. Antagonism at the 5-HT3 receptor may be of benefit in the **treatment** of **irritable bowel syndrome**. AIMS: To evaluate the effect of 12 weeks of **treatment** with **alosetron**, a **5-HT3 receptor antagonist** at doses of 0.1 mg b.d., 0.5 mg b.d. and 2 mg b.d. in **irritable bowel syndrome** patients. METHODS: A double-blind, placebo-controlled, parallel-group study with a 2-week screening and a 12-week **treatment** period was conducted. A total of 462 patients (335 female) recorded details of the severity of their abdominal pain, and bowel function daily on a diary card
throughout the study. At monthly clinic visits patients recorded the severity of their abdominal pain/discomfort and **diarrhoea** on a visual analogue scale. RESULTS: In the total population and in the female subpopulation (but not in males) **alosetron** 2 mg b.d. significantly increased the proportion of pain-free days and decreased the
visual analogue scale score for **diarrhoea** compared with placebo. **Alosetron** at doses of 0.5 mg b.d. and 2 mg b.d. led to a significant hardening of stool, and a reduction in stool frequency in the total population. CONCLUSION: **Alosetron** at a dose of 2 mg b.d. is an effective **treatment** for female patients with **irritable bowel syndrome**.

L28 ANSWER 13 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000217846 EMBASE **Irritable bowel syndrome** - **Alosetron**. Manufacturing Chemist 71/6 (23) 2000.
Refs: 5.
ISSN: 0262-4230. CODEN: MCHMDI. Pub. Country: United Kingdom. Language: English.

L28 ANSWER 14 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000063991 EMBASE **Irritable bowel syndrome** - Cilansetron. Manufacturing Chemist 71/2 (22) 2000.
Refs: 2.
ISSN: 0262-4230. CODEN: MCHMDI. Pub. Country: United Kingdom. Language: English.

L28 ANSWER 15 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
2000200552 EMBASE An update on the management of **irritable bowel syndrome**. Reilly J.P.; Howden C.W.. Dr. J.P. Reilly, Arnold/Marie Schwartz Coll. Pharm., Long Island University, Brooklyn, NY, United States. Drug Benefit Trends 12/SUPPL. B (11-16) 2000.
Refs: 42.
ISSN: 1080-5826. CODEN: DBTRFN. Pub. Country: United States. Language: English. Summary Language: English.

AB **Irritable bowel syndrome** (**IBS**) is a common, chronic disorder producing disturbances in **defecation**, abdominal pain, and bloating. While **IBS** is not considered a life-threatening disease, patients afflicted with it experience a decrease in quality of life. **IBS** is associated with significant disability, high health care costs, and decreased productivity at work. There is no single pathophysiologic marker for **IBS**. Application of diagnostic criteria and limited laboratory and clinical testing usually allow for a conclusive diagnosis. Understanding the pathophysiology and psychosocial factors in **IBS** can better prepare health care providers to improve patient outcomes. **Treatment** is based on an effective physician-patient relationship in conjunction with pharmacotherapy and behavioral modifications. The advent of new pharmacologic **therapies** acting at the 5-hyroxytryptamine receptor pathways will enable prescribers to better control **IBS** symptoms and improve quality of life.

L28 ANSWER 16 OF 69 MEDLINE
2000270511 Document Number: 20270511. **Irritable bowel syndrome**. New **treatment** drug on the market. Anonymous. HARVARD HEALTH LETTER, (2000 Jun) 25 (8) 7. Journal code: C2Y. ISSN: 1052-1577. Pub. country: United States. Language: English.

L28 ANSWER 17 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-287665 [24] WPIDS
AB WO 9917755 A UPAB: 19990624
NOVELTY - The use of a **5-HT3 receptor antagonist**, e.g. **granisetron**, or its derivative in the manufacture of a medicament for the **treatment** of non **constipated** female **irritable bowel syndrome** is new.
ACTIVITY - Antiinflammatory. In tests on female patients, those given **alosetron** (1 mg BID) reported 33.0 +/- 28.8 days with urgency compared with 54.3 +/- 32.04 days for those given placebo.
MECHANISM OF ACTION - **5-HT3 receptor antagonist.**
USE - The **5-HT3 receptor antagonist** is used to **treat irritable bowel syndrome.**

L28 ANSWER 18 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-421933 [36] WPIDS
AB FR 2773800 A UPAB: 19990908
NOVELTY - 1-Alkyl 2-(piperidinyl-methoxy, -methylthio or -methylamino) benzimidazole derivatives (I) are new.
DETAILED DESCRIPTION - 1,2-Disubstituted benzimidazole derivatives of formula (I), including enantiomers, diastereoisomers and mixtures, and their salts are new.
R1 = 1-8C alkyl (optionally substituted by OMe), cyclopropyl or (3-6C) cycloalkylmethyl;
R2 = H, halo, Me, CF3 or OMe;
X = O, S or NH;

A = 3- or 4-piperidinyl;
B' = CH2B1;
B1 = H, 1-3C alkyl (optionally substituted by OMe, CF3, NHSO2Me or p-fluorophenoxy), 3-6C cycloalkyl, phenyl or 3- or 4-pyridyl.
An INDEPENDENT CLAIM is included for the preparation of (I).
ACTIVITY - Antiemetic; neuroleptic; antidepressant; anxiolytic; anti-dementia; analgesic; gastrointestinal; antiulcer; cardiovascular; respiratory.
MECHANISM OF ACTION - 5-HT3 and 5-HT4 serotoninergic receptor antagonists. Some are selective 5-HT4 antagonists. (I) had IC50 values of 0.05-1 mu M for inhibition of in the specific bonding of (S)-**zacopride** to 5-HT3 serotoninergic receptors.
USE - For **treatment** of disorders mediated by 5-HT3 and 5-HT4 receptors, such as: nausea and vomiting (e.g. after antitumor **therapy** or administration of an anesthetic); central nervous system disorders such as schizophrenia, mania, anxiety or depression; senile dementia or Alzheimer's disease; dyskinesia, pain, migraine or headache; drug or alcohol dependence or withdrawal disorders; gastrointestinal disorders such as dyspepsia, peptic ulcers, gastric acidity or flatulence; cardiovascular and respiratory disorders; **diarrhea, irritable bowel syndrome,** esophageal reflux or intestinal motility or secretion disorders; cystic fibrosis of the pancreas; cystic fibrosis; and incontinence.
Dwg.0/0

L28 ANSWER 19 OF 69 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 6
2000:18668 Document No.: PREV200000018668. **Alosetron** relieves pain and improves bowel function compared with mebeverine in female nonconstipated **irritable bowel syndrome** patients. Jones, R. H.; Holtmann, G.; Rodrigo, L.; Ehsanullah, R. S. B.; Crompton, P. M.; Jacques, L. A.; Mills, J. G. (1). (1) Gastroenterology Clinical Development, Glaxo Wellcome Research and Development, Stockley Park West, Uxbridge, Middlesex, UB11 1BT UK. Alimentary Pharmacology & Therapeutics, (Nov., 1999) Vol. 13, No. 11, pp. 1419-1427. ISSN: 0269-2813. Language: English. Summary Language: English.
AB Background: **Irritable bowel syndrome** is one of the most common gastrointestinal disorders, yet no **therapy** convincingly controls the multiple symptoms of this syndrome. Aim: To compare the efficacy and tolerability of the new **5-HT3 -receptor antagonist alosetron** and the smooth muscle relaxant mebeverine in a double-blind, multicentre, randomized trial. Methods: Six hundred and twenty-three nonconstipated females with **irritable bowel syndrome** were randomized to receive **alosetron** 1 mg twice daily (n = 319) or mebeverine 135 mg three times daily (n = 304) for 12 weeks, followed by a 4-week post-**treatment** period. The primary efficacy end-point was monthly responders for adequate relief of **irritable bowel syndrome** related abdominal pain and discomfort (defined as patients reporting adequate relief on at least 2 out of 4 weeks). Secondary end-points included assessments of bowel function, including urgency, stool frequency and stool consistency. Results: There were significantly more responde rs in the **alosetron** group compared with mebeverine at months 2 and 3 ($P < 0.01$). Compared with mebeverine, the **alosetron** group experienced significant decreases in proportion of days with urgency and mean stool frequency, and

had firmer stools within 1 week of starting **treatment**. A similar proportion of patients reported adverse events in the two **treatment** groups. Conclusions: In nonconstipated female **irritable bowel syndrome** patients, **alosetron** is significantly more effective than mebeverine in improving symptoms.

L28 ANSWER 20 OF 69 MEDLINE DUPLICATE 7
1999397956 Document Number: 99397956. Improvement in pain and bowel function
in female irritable bowel patients with **alosetron**, a **5 -HT3 receptor antagonist**. Camilleri M; Mayer E A; Drossman D A; Heath A; Dukes G E; McSorley D; Kong S; Mangel A W; Northcutt A R. (Gastroenterology Research Unit, Mayo Foundation, Rochester, Minnesota 55905, USA.. camilleri.michael@mayol.edu) . ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1999 Sep) 13 (9) 1149-59. Journal code: A5D. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB BACKGROUND: No currently available **treatment** provides consistent relief of **irritable bowel syndrome**. Colonic sensory and motor function are modulated partly through 5HT3-receptors. AIM: To evaluate effects of the 5HT3-receptor antagonist, **alosetron**, in **irritable bowel syndrome** . METHODS: Randomized, double-blind, placebo-controlled, dose-ranging (1, 2, 4, 8 mg b.d. **alosetron**), 12-week trial in 370 patients with **diarrhoea**-predominant or alternating **constipation** and **diarrhoea irritable bowel syndrome**. Weekly measurement of adequate relief was the key end-point; other **irritable bowel syndrome** symptoms were collected daily using an electronic phone system. RESULTS: **Alosetron** (1 mg or 2 mg b.d.) significantly ($P < 0.05$ vs. placebo) increased the proportion of females, but not males, reporting adequate relief. Stool consistency, frequency and percentage days with urgency improved over placebo ($P < 0.05$) within the first month with all doses of **alosetron**, and persisted throughout the trial with all doses in female patients. With 1 mg b.d. **alosetron**, females had improved stool consistency and urgency within the first week, and adequate relief and improved stool frequency within the first 2 weeks. There was no consistent improvement in bowel function among male patients. CONCLUSION: In female **irritable bowel syndrome** patients with predominant **diarrhoea** or alternating **constipation** and **diarrhoea**, **alosetron** is effective in **treatment** of abdominal pain and discomfort and bowel-related symptoms.

L28 ANSWER 21 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999229483 EMBASE Cilansetron. **Treatment** of **IBS** 5-HT3 antagonist. Rabasseda X.; Leeson P.; Silvestre J.; Castaner J.. X. Rabasseda, Prous Science, P.O. Box 540, 08080 Barcelona, Spain. Drugs of the Future 24/5 (475-482) 1999.
Refs: 42.
ISSN: 0377-8282. CODEN: DRFUD4. Pub. Country: Spain. Language: English.

L28 ANSWER 22 OF 69 MEDLINE DUPLICATE 8
2000045407 Document Number: 20045407. **Irritable bowel**

syndrome: new pharmaceutical approaches to **treatment**.
Farthing M J. (Digestive Diseases Research Centre, St Bartholomew's & The Royal London School of Medicine & Dentistry, UK.) Baillieres Best Pract Res Clin Gastroenterol, (1999 Oct) 13 (3) 461-71. Ref: 53. Journal code: DHW. ISSN: 1521-6918. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The **irritable bowel syndrome** (**IBS**) is a consortium of symptoms including abdominal pain and alterations in the pattern of defaecation. There is no single pathophysiological marker of **IBS** although it is generally accepted that some patients do have abnormalities of intestinal motility and/or enhanced visceral sensitivity. There is also an increasing acceptance that the central nervous system, an important component of the brain-gut axis, also plays an important role in symptom production both in the response to stress and when there is an underlying affective disorder. During the past decade new **therapeutic** targets have been identified that have permitted the development of new drugs with **therapeutic** potential for **IBS**. Identification and characterization of 5-hydroxytryptamine (5-HT) receptors in the gastrointestinal tract particularly 5-HT3 and 5-HT4 receptors, which are involved not only in modulating gut motility but in visceral sensory pathways, has led to a number of studies of 5-HT3 (**Alosetron, Granisetron** and **Ondansetron**) and 5-HT4 (SB-207266A) antagonists. Both classes of drug appear to reduce visceral sensitivity and have inhibitory effects on motor activity in the distal intestine. Early clinical studies suggest that these agents may have a role in painful, **diarrhoea**-predominant **IBS**. 5-HT4 agonists (HTF919, Zelmac) may improve **constipation** -predominant **IBS** by normalizing bowel habit and thereby reducing abdominal pain. Alternative approaches to reducing visceral sensation include the use of the opioid kappa agonists, which have no central opioid effects although clinical trials have suggested that these agents are not highly effective in relieving **IBS** pain. There are in addition, new approaches to modify intestinal motility including the development of gut selective muscarinic M3 receptor antagonists such as zamifenacin and the 5-HT4 partial agonist, HTF919. Preliminary studies suggest that these agents may have **therapeutic** potential in **IBS**. Anti-depressants are increasingly used to **treat** affective disorder in **IBS** but in addition appear to have added value because of their ability to reduce visceral hypersensitivity and alter gut transit. **Therapeutic** effects are often obtained at doses below those normally used to **treat** depression. **IBS** continues to be a **therapeutic** challenge because of its diverse symptomatology and lack of a single pathophysiological target for drug intervention.

L28 ANSWER 23 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999351410 EMBASE Dealing with **irritable bowel syndrome**. Abbas Z.. Z. Abbas, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan. Journal of the Pakistan Medical Association 49/3 (78-81) 1999.
Refs: 93.
ISSN: 0030-9982. CODEN: JPKMAK. Pub. Country: Pakistan. Language: English.

L28 ANSWER 24 OF 69 MEDLINE DUPLICATE 9
1999358376 Document Number: 99358376. Review article: the safety and efficacy of **alosetron**, a **5-HT3 receptor antagonist**, in female **irritable bowel syndrome** patients. Mangel A W; Northcutt A R. (Glaxo Wellcome Inc., Research Triangle Park, North Carolina.. awm43512@glaxowellcome.com) . ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1999 May) 13 Suppl 2 77-82. Ref: 14. Journal code: A5D. ISSN: 0269-2813.
Pub. country: ENGLAND: United Kingdom. Language: English.
AB **Irritable bowel syndrome** (**IBS**) is one of the most common gastrointestinal-related conditions. In this review, the safety and efficacy of **alosetron**, a potent and selective **5-HT3 receptor antagonist**, in the **treatment** of **IBS** are discussed. **Alosetron** has been shown to produce statistically significant improvements in abdominal pain, stool consistency, stool frequency and urgency in female **IBS** patients. By contrast, no consistent improvement has been seen in male **IBS** patients **treated** with **alosetron**. The only adverse event of note with **alosetron** was **constipation**, and this represents a class effect of **5-HT3 receptor antagonists**. In conclusion, **alosetron** is a safe and effective **treatment** for female **IBS** patients.

L28 ANSWER 25 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999165813 EMBASE The safety and efficacy of **alosetron**, a **5-HT3 receptor antagonist**, in female **irritable bowel syndrome** patients. Mangel A.W.; Northcutt A.R.. Dr. A.W. Mangel, Glaxo Wellcome Inc., 5 Moore Drive, Research Triangle Park, NC 27709, United States. awm43512@glaxowellcome.com. Alimentary Pharmacology and Therapeutics, Supplement 13/2 (77-82) 1999.
Refs: 14.
ISSN: 0953-0673. CODEN: ATSLEO. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB **Irritable bowel syndrome** (**IBS**) is one of the most common gastrointestinal-related conditions. In this review, the safety and efficacy of **alosetron**, a potent and selective **5-HT3 receptor antagonist**, in the **treatment** of **IBS** are discussed. **Alosetron** has been shown to produce statistically significant improvements in abdominal pain, stool consistency, stool frequency and urgency in female **IBS** patients. By contrast, no consistent improvement has been seen in male **IBS** patients **treated** with **alosetron**. The only adverse event of note with **alosetron** was **constipation**, and this represents a class effect of **5-HT3 receptor antagonists**. In conclusion, **alosetron** is a safe and effective **treatment** for female **IBS** patients.

L28 ANSWER 26 OF 69 MEDLINE
1999219992 Document Number: 99219992. Management of **irritable bowel syndrome**: novel approaches to the pharmacology of

gut motility. Scarpignato C; Pelosini I. (Department of Gastroenterology and Hepatology, Faculty of Medicine, University of Nantes, France.. scarpi@tin.it) . CANADIAN JOURNAL OF GASTROENTEROLOGY, (1999 Mar) 13 Suppl
A 50A-65A. Ref: 169. Journal code: CR9. ISSN: 0835-7900. Pub. country: Canada. Language: English.

AB Although it is unclear to what extent **irritable bowel syndrome** (**IBS**) symptoms represent a normal perception of abnormal function or an abnormal perception of normal function, many believe that **IBS** constitutes the clinical expression of an underlying motility disorder, affecting primarily the mid- and lower gut. Indeed, transit and contractile abnormalities have been demonstrated with sophisticated techniques in a subset of patients with **IBS**. As a consequence, drugs affecting gastrointestinal (GI) motility have been widely employed with the aim of correcting the major **IBS** manifestations, ie, pain and altered bowel function. Unfortunately, no single drug has proven to be effective in **treating IBS** symptom complex. In addition, the use of some medications has often been associated with unpleasant side effects. Therefore, the search for a truly effective and safe drug to control motility disturbances in **IBS** continues. Several classes of drugs look promising and are under evaluation. Among the motor-inhibiting drugs, gut selective muscarinic antagonists (such as zamifenacin and darifenacin), neurokinin2 antagonists (such as MEN-10627 and MEN-11420), beta3-adrenoreceptor agonists (eg, SR-58611A) and GI-selective calcium channel blockers (eg, pinaverium bromide and octylonium) are able to decrease painful contractile activity in the gut (antispasmodic effect), without significantly affecting other body functions. Novel mechanisms to stimulate GI motility and transit include blockade of cholecystokinin (CCK)A receptors and stimulation of motilin receptors. Loxiglumide (and its dextroisomer, dexloxiglumide) is the only CCKA receptor antagonist that is being evaluated clinically. This drug accelerates gastric emptying and colonic transit, thereby increasing the number of bowel movements in patients with chronic **constipation**. It is also able to reduce visceral perception. Erythromycin and related 14-member macrolide compounds inhibit the binding of motilin to its receptors on GI smooth muscle and, therefore, act as motilin agonists. This antibiotic accelerates gastric emptying and shortens orocecal transit time. In the large bowel a significant decrease in transit is observed only in the right colon, which suggests a shift in fecal distribution. Several 'motilinomimetics' have been synthesized. Their development depends on the lack of antimicrobial activity and the absence of fading of the prokinetic effect during prolonged administration. 5-hydroxytryptamine (5-HT)4 agonists with significant pharmacological effects on the mid- and distal gut (such as prucalopride and tegaserod) are available for human use. These 'enterokinetic' compounds are useful for **treating constipation** -predominant **IBS** patients. **5-HT3 receptor antagonists** also possess a number of interesting pharmacological properties that may make them suitable for **treatment** of **IBS**. Besides decreasing colonic sensitivity to distension, these drugs prolong intestinal transit and may be particularly useful in **diarrhea**-predominant **IBS**.

Finally, when administered in small pulsed doses, octreotide, besides reducing the perception of rectal distension, accelerates intestinal transit, although other evidence disputes such an effect.

L28 ANSWER 27 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999165808 EMBASE Clinical evidence to support current **therapies** of **irritable bowel syndrome**. Camilleri M.. Prof.
M. Camilleri, GI Unit, Mayo Clinic, Rochester, MN 55905, United States. camilleri.michael@mayo.edu. Alimentary Pharmacology and Therapeutics, Supplement 13/2 (48-53) 1999.
Refs: 60.
ISSN: 0953-0673. CODEN: ATSLEO. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB This review summarizes the clinical evidence to support current **therapies** in **irritable bowel syndrome** (**IBS**). Fibre is indicated at a dose of at least 12 g per day in patients with **constipation**-predominant **IBS**. Loperamide (and probably other opioid agonists) are of proven benefit in **diarrhoea**-predominant **IBS**: loperamide may also aid continence by enhancing resting anal tone. In general, smooth muscle relaxants are best used sparingly, on an 'as needed' basis, as their overall efficacy is unclear. Psychotropic agents are important in relieving depression and of proven benefit for pain and **diarrhoea** in patients with depression associated with **IBS**. Further trials with selective serotonin reuptake inhibitors (SSRIs) are awaited. Psychological **treatments** including hypnotherapy are less widely available, but may play an important role in relief of pain. In summary, current **therapies** targeted on the predominant symptoms in **IBS** are moderately successful. New **therapies** are needed to more effectively relieve this syndrome, not just symptoms.

L28 ANSWER 28 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999094554 EMBASE Tegaserod Maleate. 5-HT4 agonist, prokinetic, **treatment** of **irritable bowel syndrome**
. Graul A.; Silvestre J.; Castaner J.. A. Graul, Prous Science, P.O. Box 540, 08080 Barcelona, Spain. Drugs of the Future 24/1 (38-44) 1999.
Refs: 31.
ISSN: 0377-8282. CODEN: DRFUD4. Pub. Country: Spain. Language: English.

L28 ANSWER 29 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999404971 EMBASE Patient subgroups in **irritable bowel syndrome** that can be defined by symptom evaluation and physical examination. Whitehead W.E.. Dr. W.E. Whitehead, Department of Medicine, Division of Digestive Diseases, University of North Carolina, Chapel Hill,
NC 27599-7080, United States. American Journal of Medicine 107/5 SUPPL. 1
(33-40) 1999.
Refs: 72.
ISSN: 0002-9343. CODEN: AJMEAZ.
Publisher Ident.: S 0002-9343(99)00078-9. Pub. Country: United States. Language: English. Summary Language: English.
AB Subgroups of patients with **irritable bowel syndrome** (**IBS**) are likely to respond differently to existing and evolving **therapies**. The following criteria for subgrouping may be considered: (1) Patients with different predominant

bowel habits respond differently to **treatment** (antidepressants, 5HT3-antagonists, psychotherapy). (2) Postprandial exacerbation of pain or other gastrointestinal symptoms is seen in approximately half of patients with **IBS** and may identify patients who are more responsive to some classes of drugs (e.g., those targeted at motility). (3) Women appear to respond differently from men to 5HT3-antagonists, and there may be gender differences in gastrointestinal physiology. (4) There is more overlap in the diagnosis of functional dyspepsia and **IBS** than would be predicted by chance, and both are associated with hyperalgesia to intraluminal distention. Copyright (C) 1999 Excerpta Medica Inc.

L28 ANSWER 30 OF 69 MEDLINE DUPLICATE 10
1999358369 Document Number: 99358369. Review article: the **therapeutic** potential of **5-HT3 receptor antagonists** in the **treatment** of **irritable bowel syndrome**. Humphrey P P; Bountra C; Clayton N; Kozlowski K. (Glaxo Institute of Applied Pharmacology, Department of Pharmacology, University of Cambridge, UK.. ppah0562@glaxowellcome.co.uk) . ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1999 May) 13 Suppl 2 31-8. Ref: 70. Journal code: A5D. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom. Language: English.
AB There is evidence from studies, in both animals and humans, that 5-HT3 receptor blockade has potential value in the **treatment** of **irritable bowel syndrome**, particularly in those patients with **diarrhoea**-predominant bowel habits. New findings suggest that 5-HT3 receptors exist on gut afferent neurones and that their activation by locally released 5-HT leads to visceral nociceptive stimulation, in addition to increased neuronally-mediated motor and secretory activity. If this concept is validated, it will provide a rationale for the use of **5-HT3 receptor antagonists** in patients with increased gut motility, reduced fluid absorption and low nociceptive thresholds leading to abdominal pain. **Alosetron** is a highly selective, potent **5-HT3 receptor antagonist** which is well absorbed with a long pharmacodynamic half-life. Its ability to provide long-lasting blockade of 5-HT3 receptors throughout the body make it an ideal candidate within its class to evaluate the clinical hypothesis that sustained and ubiquitous 5-HT3 receptor blockade is of value in the **treatment** of **IBS**.

L28 ANSWER 31 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999165806 EMBASE The **therapeutic** potential of **5-HT3 receptor antagonists** in the **treatment** of **irritable bowel syndrome** . Humphrey P.P.A.; Bountra C.; Clayton N.; Kozlowski K.. Prof. P.P.A. Humphrey, Glaxo Institute Applied Pharmacology, Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QJ, United Kingdom. ppah0562@glaxowellcome.co.uk. Alimentary Pharmacology and Therapeutics, Supplement 13/2 (31-38) 1999.
Refs: 70.
ISSN: 0953-0673. CODEN: ATSLEO. Pub. Country: United Kingdom. Language:

English. Summary Language: English.

AB There is evidence from studies, in both animals and humans, that 5-HT3 receptor blockade has potential value in the **treatment** of **irritable bowel syndrome**, particularly in those patients with **diarrhoea**-predominant bowel habits. New findings suggest that 5-HT3 receptors exist on gut afferent neurones and that their activation by locally released 5-HT leads to visceral nociceptive stimulation, in addition to increased neuronally-mediated motor and secretory activity. If this concept is validated, it will provide a rationale for the use of **5-HT3 receptor antagonists** in patients with increased gut motility, reduced fluid absorption and low nociceptive thresholds leading to abdominal pain. **Alosetron** is a highly selective, potent **5-HT3 receptor antagonist** which is well absorbed with a long pharmacodynamic half-life. Its ability to provide long-lasting blockade of 5-HT3 receptors throughout the body make it an ideal candidate within its class to evaluate the clinical hypothesis that sustained and ubiquitous 5-HT3 receptor blockade is of value in the **treatment** of **IBS**.

L28 ANSWER 32 OF 69 MEDLINE DUPLICATE 11

2000053391 Document Number: 20053391. **Therapeutic** approach to the patient with **irritable bowel syndrome**.

Camilleri M. (Department of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota 55905, USA.) AMERICAN JOURNAL OF MEDICINE, (1999 Nov 8) 107 (5A) 27S-32S. Ref: 54. Journal code: 3JU. ISSN: 0002-9343. Pub. country: United States. Language: English.

AB This article reviews briefly the evidence to support current **therapies** in **irritable bowel syndrome** (**IBS**) and the novel **therapeutic** approaches on the threshold of clinical application. Fiber is indicated at a dose of at least 12 grams per day in patients with **constipation**-predominant **IBS**. Loperamide (and probably other opioid agonists) are of proven benefit in **diarrhea**-predominant **IBS**; loperamide may also aid continence by enhancing resting anal tone, but there is no evidence that it results in pain relief. In general, smooth muscle relaxants are best used sparingly, on an as-needed basis, because their overall efficacy is unclear. The 5-HT3 antagonist, **alosetron**, results in adequate relief of pain and improvements in bowel function in female nonconstipated patients with **IBS**. Psychotropic agents are important in relieving depression and are of proven benefit for pain and **diarrhea** in patients with depression associated with **IBS**. Further trials with selective serotonin reuptake inhibitors are awaited.

Psychological **treatments** including hypnotherapy are less widely available but may play an important role in the relief of pain. In summary, current **therapies** targeted on the predominant symptoms in **IBS** are moderately successful. As the bowel sensorimotor and limbic system disturbances of **IBS** are more clearly understood, we should anticipate other pharmacologic approaches in the near future, including alpha-adrenergic agonists and 5-HT4 agonists. New **therapies** directed at **treatment** of the syndrome, rather than relief of symptoms, are needed.

L28 ANSWER 33 OF 69 CAPLUS COPYRIGHT 2000 ACS
1999:812148 Document No. 132:44368 **Therapeutic** approach to the patient with **irritable bowel syndrome**.
Camilleri, Michael (Departments of Medicine and Physiology, Mayo Clinic and Mayo Foundation, Rochester, MI, USA). Am. J. Med., 107(5A), 27S-32S (English) 1999. CODEN: AJMEAZ. ISSN: 0002-9343. Publisher: Excerpta Medica, Inc..
AB A review with 54 refs. This article reviews briefly the evidence to support current **therapies** in **irritable bowel syndrome** (**IBS**) and the novel **therapeutic** approaches on the threshold of clin. application. Fiber is indicated at a dose of at least 12 g per day in patients with **constipation** -predominant **IBS**. Loperamide (and probably other opioid agonists) are of proven benefit in **diarrhea**-predominant **IBS**; loperamide may also aid continence by enhancing resting anal tone, but there is no evidence that it results in pain relief. In general, smooth muscle relaxants are best used sparingly, on an as-needed basis, because their overall efficacy is unclear. The 5-HT3 antagonist, **alosetron**, results in adequate relief of pain and improvements in bowel function in female nonconstipated patients with **IBS**. Psychotropic agents are important in relieving depression and are of proven benefit for pain and **diarrhea** in patients with depression assocd. with **IBS**. Further trials with selective serotonin reuptake inhibitors are awaited. Psychol. **treatments** including hypnotherapy are less widely available but may play an important role in the relief of pain. In summary, current **therapies** targeted on the predominant symptoms in **IBS** are moderately successful. As the bowel sensorimotor and limbic system disturbances of **IBS** are more clearly understood, we should anticipate other pharmacol. approaches in the near future, including .alpha.-adrenergic agonists and 5-HT4 agonists. New **therapies** directed at **treatment** of the syndrome, rather than relief of symptoms, are needed.

L28 ANSWER 34 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999142730 EMBASE The role of the mental health professional in the assessment and management of **irritable bowel syndrome**. Gaynes B.N.; Drossman D.A.. Dr. B.N. Gaynes, Psychiat. Consultation/Liaison Svc., Department of Psychiatry, University of North Carolina, Chapel Hill, NC, United States. CNS Spectrums 4/4 (19-30) 1999.
Refs: 73.
ISSN: 1092-8529. CODEN: CNSPFH. Pub. Country: United States. Language: English. Summary Language: English.
AB **Irritable bowel syndrome** (**IBS**), a condition common in the health-care setting, can be especially challenging to manage for both the referring physician and the psychiatrist. Much of this difficulty arises from the understanding and **treatment** of the disorder from a disease-based biomedical approach rather than a biopsychosocial model. The latter model offers a more effective method to understand the development and clinical expression of **IBS**, and as a result, directly informs subsequent management. This article defines and describes the epidemiology of **IBS**, reviews its pathophysiology, identifies the role of psychosocial factors using a biopsychosocial model of **IBS**, and clarifies the role of the

mental health professional in its management. **IBS** management involves identifying psychiatric comorbidities, assessing the patient's perspective of the role of psychosocial factors, offering psychotherapy directed toward adaptive coping mechanisms, providing psychotropic medication consultation, and engaging in ongoing collaboration with the referring physician.

L28 ANSWER 35 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999096434 EMBASE New horizons in the **treatment** of **irritable bowel syndrome**. Bamba T.; Fuse K..
Dr. T. Bamba, Second Dept. of Internal Medicine, Shiga University of Medical Science, Tsukinowa, Seta, Ohtsu 520-2192, Japan. Drugs of Today 35/1 (5-12) 1999.
Refs: 20.
ISSN: 0025-7656. CODEN: MDACAP. Pub. Country: Spain. Language: English. Summary Language: English.
AB **Irritable bowel syndrome** is one of the most common diseases in gastroenterology clinics. Bowel movement is controlled by many factors such as gastrointestinal hormones and gut brain system, which are too complicated to evaluate by clinical investigation. Therefore, lBS is diagnosed on the basis of the Rome diagnostic criteria, after excluding organic gastrointestinal diseases. The basic principle in the **therapy** of lBS is to centrally stabilize the mental state and locally normalize intestinal function, in addition to regular daily life and dietary guidance.

L28 ANSWER 36 OF 69 MEDLINE DUPLICATE 12
1998350160 Document Number: 98350160. Benzoxazole derivatives as novel 5-HT3 receptor partial agonists in the gut. Sato Y; Yamada M; Yoshida S; Soneda T; Ishikawa M; Nizato T; Suzuki K; Konno F. (Pharmaceutical Research Center, Meiji Seika Kaisha, 760 Morooka-Cho, Kohoku-ku, Yokohama 222, Japan.) JOURNAL OF MEDICINAL CHEMISTRY, (1998 Jul 30) 41 (16) 3015-21.
Journal code: JOF. ISSN: 0022-2623. Pub. country: United States. Language:
English.
AB A series of benzoxazoles with a nitrogen-containing heterocyclic substituent at the 2-position was prepared and evaluated for 5-HT3 partial agonist activity on isolated guinea pig ileum. The nature of the substituent at the 5-position of the benzoxazole ring affected the potency for the 5-HT3 receptor, and the 5-chloro derivatives showed increased potency and lowered intrinsic activity. 5-Chloro-7-methyl-2-(4-methyl-1-homopiperazinyl)benzoxazole (6v) exhibited a high binding affinity in the same range as that of the 5-HT3 antagonist **granisetron**, and its intrinsic activity was 12% of that of 5-HT. Compound 6v inhibited 5-HT-evoked **diarrhea** but did not prolong the transition time of glass beads in the normal distal colon even at a dose of 100 times the ED50 for **diarrhea** inhibition in mice. Compounds of this type are expected to be effective for the **treatment** of **irritable bowel syndrome** without the side effect of **constipation**.

L28 ANSWER 37 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999030118 EMBASE Motility disorders in childhood. Milla P.J.. Prof. P.J.

Milla, Institute of Child Health, University of London, 30 Guilford Street, London WC1N 1EH, United Kingdom. Bailliere's Clinical Gastroenterology 12/4 (775-797) 1998.
Refs: 68.
ISSN: 0950-3528. CODEN: BCGAER. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Motility disorders are very common in childhood, causing a number of gastrointestinal symptoms: recurrent vomiting, abdominal pain and distension, **constipation** and obstipation, and loose stools. The disorders result from disturbances of gut motor control mechanisms caused by either intrinsic disease of nerve and muscle, central nervous system dysfunction or perturbation of the humoral environment in which they operate. Intrinsic gut motor disease and central nervous system disorder are most usually congenital in origin, and alterations of the humoral environment acquired. **Irritable bowel syndrome** occurs in children as well as adults and is multifactorial in origin, with an interplay of psychogenic and organic disorders.

L28 ANSWER 38 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998133143 EMBASE Colonic sensorimotor physiology in health, and its alteration in **constipation** and **diarrhoeal** disorders.
Camilleri M.; Ford M.J.. Dr. M. Camilleri, Mayo Clinic, GI Unit-Alfred 2-435, 200 First Street SW, Rochester, MN 55905, United States.
Alimentary Pharmacology and Therapeutics 12/4 (287-302) 1998.
Refs: 135.
ISSN: 0269-2813. CODEN: APTHEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Aim: To review the physiology of colonic motility and sensation in health humans and the pathophysiological changes associated with **constipation** and **diarrhea**. Source: Medline Search from 1965 using the index terms: human, colonic motility, sensation, pharmacology, neurohormonal control, gastrointestinal transit, **constipation**, **diarrhoea** and combinations of these.
Results: In health, the ascending and transverse regions of colon function as reservoirs to accommodate ileal chyme and the descending colon acts as a conduit: the neuromuscular functions and transmitters control colonic motility and sensation and play pivotal roles in disorders associated with **constipation** and/or **diarrhoea**. Disorders of proximal colonic transit contribute to symptoms in idiopathic **constipation**, **diarrhoea**-predominant **irritable bowel syndrome** and carcinoid **diarrhoea**. Colonic function in patients presenting with **constipation** is best assessed clinically by colonic transit time using radiopaque markers ingested orally. Measurements of colonic contractility are less useful clinically but they can help identify motor abnormalities including colonic inertia; in some patients with **irritable bowel syndrome**, abdominal pain, urgency and **diarrhoea** are temporally associated with high amplitude contractions, which originate in the proximal colon and traverse the distal conduit at very high propagation velocities. Visceral hypersensitivity contributes to the urgency and tenesmus in **irritable bowel syndrome** and inflammatory bowel disease. Colonic motility and sensation can be reduced

by anticholinergic agents, somatostatin analogues and 5HT3 antagonists. Conclusion: Physiological and pharmacological studies of the human colon have provided new insights into the pathophysiology of colonic disorders, and offer possibilities of novel **therapeutic** approaches for **constipation** or **diarrhoea** associated with colonic motor or sensory dysfunction.

L28 ANSWER 39 OF 69 MEDLINE DUPLICATE 13
1998328897 Document Number: 98328897. New drugs in the management of the **irritable bowel syndrome**. Farthing M J.
(Digestive Diseases Research Centre, St Bartholomew's, London, England.. m.farthing@mds.qmw.ac.uk) . DRUGS, (1998 Jul) 56 (1) 11-21. Ref: 50. Journal code: EC2. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB **Irritable bowel syndrome** (**IBS**) continues to provide a major **therapeutic** challenge to clinicians and those involved in drug development. It seems unlikely from the data before us that this multisymptom syndrome with peripheral and central components is likely to respond reliably in all patients to the same single agent. There is still a lack of well designed, appropriately powered, randomised clinical trials and the problems of dealing with the high placebo response rate in this group of patients remains a dilemma for trial designers. There are, however, some new ideas, particularly those relating to the role of hyperalgesia in **IBS**. For many patients, abdominal pain and bloating are the most distressing symptoms of this disease and the new drugs targeted at pain control, such as kappa agonists and serotonin antagonists (5-HT3) and possibly 5-HT4), may eventually find a place in the clinical management of this syndrome. Other candidates include somatostatin analogues and antidepressants, the latter predominantly for their effects on increasing pain threshold. More speculative new drugs for **IBS** include cholecystokinin antagonists such as loxiglumide and the gonadotrophin-releasing hormone analogue, leuprorelin (leuprolide). The results of on-going randomised clinical trials are still awaited for some of these newer agents. The **irritable bowel syndrome** (**IBS**) is the most common gastrointestinal condition encountered by general practitioners and is reported to account for up to 50% of the work of gastroenterologists in secondary care. However, most people with the symptoms of **IBS** (60 to 75%) do not consult a doctor. Its cause is unknown, its development is poorly understand and, perhaps not surprisingly, no universally agreed approach to **treatment** exists.

L28 ANSWER 40 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
96070429 EMBASE Document No.: 1996070429. Gastrointestinal motility disorders. Abell T.L.; Werkman R.F.. Division of Gastroenterology, College of Medicine, University of Tennessee, 951 Court Ave.,Memphis, TN 38163, United States. American Family Physician 53/3 (895-902) 1996. ISSN: 0002-838X. CODEN: AFPYAE. Pub. Country: United States. Language: English. Summary Language: English.

AB A careful history can localize gastrointestinal motility disorders end suggest appropriate diagnostic tests. Dysphagia, odynophagia, heartburn

and reflux have esophageal origins. The same symptoms occur in achalasia, a classic motor disorder of the lower esophageal sphincter, which can be diagnosed by barium swallow, endoscopy and esophageal motility studies. Nausea, vomiting, anorexia, bloating and abdominal pain are symptoms of motor disorders of the stomach and small intestine. When these symptoms are accompanied by unexplained right upper quadrant pain, elevated liver enzyme levels and unexplained recurrent pancreatitis, the diagnosis of impaired biliary motility is suggested. Colorectal motility disorders may present as abdominal pain, **diarrhea**, **constipation** and/or fecal incontinence. If symptoms do not resolve with dietary changes and appropriate medications and the anatomy is normal on lower gastrointestinal studies, colorectal motility studies may be indicated.

L28 ANSWER 41 OF 69 MEDLINE DUPLICATE 14

97081306 Document Number: 97081306. **Ondansetron**. A review of its pharmacology and preliminary clinical findings in novel applications. Wilde M I; Markham A. (Adis International Limited, Auckland, New Zealand.) DRUGS, (1996 Nov) 52 (5) 773-94. Ref: 185. Journal code: EC2. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB The use of **ondansetron**, a selective serotonin 5-**HT3 receptor antagonist**, is well established in patients with nausea and vomiting associated with cancer chemotherapy, radiotherapy or anaesthesia and surgery. The wide distribution of 5-HT3 receptors in the body and the role of these receptors in disease have provided the rationale for investigation of **ondansetron** in novel applications. Preliminary data have shown **ondansetron** to have clinical benefit in patients with nausea and vomiting associated with drug overdosage or poisoning, anti-infective or antidepressant **therapies**, uraemia or neurological trauma, and in patients with pruritus. Patients with gastrointestinal motility disorders (e.g. carcinoid syndrome, **irritable bowel syndrome**, **diarrhoea** associated with cryptosporidiosis or diabetes, and chronic refractory **diarrhoea**) have also shown some improvement when **treated** with **ondansetron**, as have patients with certain pain or CNS-related disorders [e.g. alcohol (ethanol) dependence, opiate withdrawal, vertigo, cerebellar tremor and Parkinson's disease **treatment**-related psychosis]. In contrast to conventional antiemetics, **ondansetron** is generally well tolerated with a lower incidence of sedation and only isolated case reports of extrapyramidal reactions. Furthermore, unlike dopamine receptor-blocking neuroleptics, **ondansetron** does not appear to worsen the symptoms of Parkinson's disease. Thus, in addition to its established indications, preliminary results suggest that **ondansetron** may be beneficial in a number of novel applications. This drug may represent a **treatment** alternative in patients with refractory disease, or an effective **treatment** of conditions for which current **therapies** are either poorly tolerated or not available. Further investigation of **ondansetron** in a range of potential new applications appears to be warranted.

L28 ANSWER 42 OF 69 MEDLINE DUPLICATE 15

97006471 Document Number: 97006471. Selective 5-hydroxytryptamine antagonism: a role in **irritable bowel syndrome** and functional dyspepsia?. Maxton D G; Morris J; Whorwell P J. (Department

IWIDS

of Medicine, University Hospital of South Manchester, Didsbury, UK.)
ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1996 Aug) 10 (4) 595-9.
Journal code: A5D. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom.
Language: English.

AB BACKGROUND: Abnormalities of gut motility and visceral pain perception are both thought to be involved in the pathogenesis of **irritable bowel syndrome** and may be susceptible to modulation by drugs affecting the various 5-HT receptor subtypes. The aim of this study was to investigate the **therapeutic** potential of a 5-HT3 antagonist in **irritable bowel syndrome**. METHODS: Fifty patients with **irritable bowel syndrome** were **treated** with **ondansetron**, a highly selective 5-HT3 antagonist, in a double-blind, placebo-controlled cross-over study. In addition to assessing its effect on the classical symptoms of **irritable bowel syndrome** (abdominal pain, distension and disordered bowel habit) its effect on symptoms often seen in **irritable bowel syndrome**, but more commonly associated with functional dyspepsia, was also examined. RESULTS: **Ondansetron** reduced bowel frequency (P = 0.035) and improved stool consistency (P = 0.002) in **diarrhoea** predominant **irritable bowel syndrome** and did not cause a deterioration of bowel habit in **constipation** predominant subjects. No statistically significant improvement was seen for abdominal pain or distension, although those patients who did respond were approximately twice as likely to be taking **ondansetron** than placebo. It was also found that **ondansetron** significantly improved the upper gastrointestinal symptoms of post-prandial epigastric discomfort (P = 0.008), flatulence (P = 0.022) and heartburn (P = 0.003). CONCLUSION: The results of this study justify evaluation of the **therapeutic** potential of selective 5-HT antagonists in both functional dyspepsia and **irritable bowel syndrome**.

L28 ANSWER 43 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
96350719 EMBASE Document No.: 1996350719. Modification of visceral sensitivity and pain in **irritable bowel syndrome** by 5-HT3 antagonism (**ondansetron**). Goldberg P.A.; Kamm M.A.; Setti-Carraro P.; Van der Sijp J.R.M.; Roth C.. Physiology Unit, St Mark's Hospital, Watford Road,Harrow HA1 3UJ, United Kingdom. Digestion 57/6 (478-483) 1996.
ISSN: 0012-2823. CODEN: DIGEBW. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Intrinsic neurons containing serotonin (5-HT) are involved in the regulation of gastrointestinal motor function and are also thought to be important in the modulation of visceral sensory function. We have evaluated the effect of a specific 5-HT3 antagonist (**ondansetron**, O) on visceral sensation and rectal compliance in a randomized, double-blind, cross-over, placebo (P) controlled study of O 16 mg 3 times/day, in healthy volunteers and patients with **irritable bowel syndrome** (**IBS**). Symptoms were also evaluated in the latter group. A 2-week run-in period was followed by two 2-week **treatment** arms of P and O, separated by a 2-week wash-out period. Twelve healthy subjects and 9 patients with **IBS** were

recruited. Assessment was by daily symptom and bowel function diary, and physiological tests of anal manometry, rectal sensory testing to distension and electrical stimulation, and rectal compliance. Ten healthy subjects completed the entire study, and 6 **IBS** patients completed the diary card evaluation, including 5 who also completed the physiological evaluation. O caused significantly ($p < 0.01$) firmer stools when considering both subject groups together. In the healthy subjects no physiological parameters were altered by O. In **IBS** patients the rectal sensory threshold to electrical stimulation tended to increase with O (20 vs. 28 mA, P vs. O, median, $p = 0.06$) while the urge (80 vs. 60 ml, $p = 0.05$) and maximum tolerated volumes (130 vs. 90, $p = 0.03$) to distension tended to decrease with O. Patients with **IBS** experienced significantly fewer daily episodes of pain while on O (2 vs. 1, $p = 0.03$). Serotonin-3 antagonism (O) causes firmer bowel actions in all subjects, and may affect gut sensitivity and pain in patients with **IBS**.

L28 ANSWER 44 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

96370199 EMBASE Document No.: 1996370199. 5-Hydroxytryptamine and functional bowel disorders. Sanger G.J.. SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Third Avenue,Harlow CM19 5AW, United Kingdom. Neurogastroenterology and Motility 8/4 (319-331) 1996. ISSN: 1350-1925. CODEN: NMOTEK. Pub. Country: United Kingdom. Language: English. Summary Language: English.

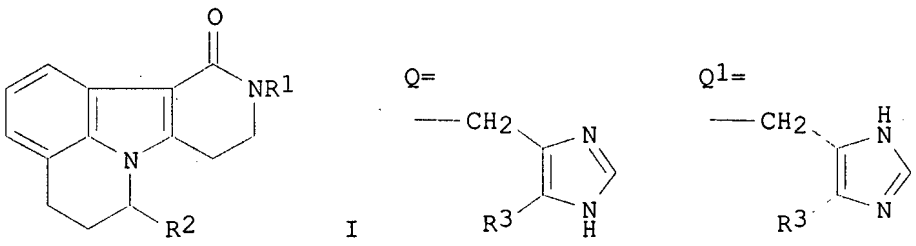
AB The possibility that 5-hydroxytryptamine (5-HT) acts as a key sensitising agent in the aetiology of **irritable bowel syndrome** (**IBS**) is reviewed. The strategic locations of 5-HT and its receptors are described, the most dominant being the 5-HT3 and 5-HT4 type. 5-HT, acting mostly at 5-HT3 or 5-HT3-like receptors, enhances the sensitivity of visceral neurones projecting between the gut and the central nervous systems. 5-HT, acting at 5-HT4 receptors promotes the sensitivity of enteric neurones that react to luminal stimuli. 5-HT4 and 5-HT3 receptors also mediate, respectively, sensitizing and physiological actions of 5-HT on gastrointestinal motor and secretory functions. This distribution implies that some **5-HT3 receptor antagonists** might reduce certain symptoms of **IBS**, such as pain, by reducing the reactivity of the visceral afferent neurones linking the gut with the brain and spinal cord. However, such antagonists are not likely to find widespread clinical acceptance because they can also affect normal lower bowel function and promote **constipation**. 5-HT4 receptor antagonists, by contrast, reduce 5-HT-induced enteric nerve hypersensitivity without notably affecting the function of the normal bowel. Accordingly these agents may reduce the symptoms of **IBS** directly, by reducing the incidence of **defecation** and **diarrhoea** and indirectly, by reducing both 'rebound' **constipation** and the post-prandial discomfort and pain associated with gastrointestinal hyper-reactivity.

L28 ANSWER 45 OF 69 BIOSIS COPYRIGHT 2000 BIOSIS

1995:545957 Document No.: PREV199698560257. **Irritable bowel syndrome**: Current **therapeutic** approach. Olmos, Jorge. Acta Gastroenterologica Latinoamericana, (1995) Vol. 25, No. 3, pp. 183-184. ISSN: 0300-9033. Language: Spanish.

L28 ANSWER 46 OF 69 CAPLUS COPYRIGHT 2000 ACS DUPLICATE 16
1995:780316 Document No. 123:169623 Preparation of indole derivatives as antagonists of serotonin 5-HT3 receptor. Tsuchiya, Shinji; Yasuda, Noboyuki; Fukuzaki, Atsushi (Tokyo Tanabe Co. Ltd., Japan). PCT Int. Appl. WO 9511245 A1 19950427, 29 pp. DESIGNATED STATES: W: AU, CA, JP, KR, US; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1994-JP1769 19941020. PRIORITY: JP 1993-261997 19931020.

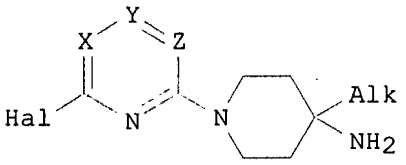
GI



AB (Imidazolylmethyl)pyrido[3',4':4,5]pyrrolo[3,2,1-ij]quinoline derivs. represented by general formula (I; R1 = Q, Q1; R2 = (un)substituted Ph; R3 = H, Me or Et), isomers thereof or a mixt. of the isomers, a physiol. acceptable salt thereof, and a solvate thereof are prepd. These compds. I have a long-lasting, potent, and selective antagonism against intestinal 5-HT3 receptors when compared with known 5-HT3 antagonists and are particularly useful for preventing or **treating** digestive tract disorders such as **irritable bowel syndrome** and **diarrhea**. Thus, 650 mg I (R1 = H, R2 = Ph) (prepn. given) and 960 mg 4-(chloromethyl)-5-methyl-1-trityl-1H-imidazole were dissolved in DMF and **treated** with 120 mg 55% NaH at room temp. overnight to give, after detritylation with AcOH in refluxing aq. THF, I (R1 = Q, wherein R3 = Me; R2 = Ph) (II). II in vitro inhibited the 2-methylserotonin-induced contraction of a Hartley guinea pig colon with PA2 value of 9.4 vs. 6.6, 8.4, 7.7, and 8.0 for known antagonists such as **ondansetron** hydrochloride, YM-060, **alosetron** hydrochloride, and I (R1 = Q, wherein R3 = Me; R2 = H) (compd. A), resp. II at 10 .mu.g/kg p.o. inhibited the stress-induced **diarrhea** in Wister mice by 50% vs. 30 and 20% for YM-060 and compd. A, resp.

L28 ANSWER 47 OF 69 CAPLUS COPYRIGHT 2000 ACS
1995:568637 Document No. 122:314578 Heteroarylpiperidines, process for their preparation, and pharmaceutical compositions containing them.. Baroni, Marco; Croci, Tiziano; Landi, Marco; Guzzi, Umberto; Nisato, Dino (Sanofi, Fr.; Midy S.p.A.). Eur. Pat. Appl. EP 647639 A1 19950412, 13 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE. (French). CODEN: EPXXDW. APPLICATION: EP 1994-402262 19941010. PRIORITY: EP 1993-402498 19931011.

GI



I

AB Title compds. I [Hal = halogen; Alk = C1-4 alkyl; X, Y, Z = CH, or 2 of them are CH and 1 is N] and their salts are claimed. The compds. are powerful and selective 5-HT3 receptor agonists (no data), and are claimed useful for **treatment** of depression, psychosis, anxiety, intestinal motility disorders, etc. For example, reaction of 1-benzyl-4-methyl-1,2,3,6-tetrahydropyridine with MeCN in concd. H2SO4 at 70.degree. gave 1-benzyl-4-(acetylamino)-4-methylpiperidine, which underwent debenzylation using H2 and Pd/C catalyst, condensation with 2,6-dichloropyridine in n-pentanol in the presence of K2CO3, and deacetylation using refluxing 6M HCl, to give I [Hal = Cl, Alk = Me, X = Y = Z = CH] as the HCl salt.

L28 ANSWER 48 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1995-147379 [19] WPIDS
CR 1995-147378 [19]
AB WO 9509168 A UPAB: 19950524
Indoline cpds. of formula (I) and their salts and solvates are new. R1 = indoline gp; R2 = phenyl or aromatic heterocyclic (both opt. substd.); R3 = H, halogen, lower alkyl, OH, lower alkoxy, carbamoyl or lower alkoxy carbonyl.

USE - (I) are **5-HT3 receptor antagonists** useful for the prevention and **treatment** of vomiting or nausea induced by chemotherapy or radiation, **irritable bowel syndrome** and **diarrhoea**.

ADVANTAGE - (I) exhibit potent **5-HT3 receptor antagonist** activity in the intestinal tract, in comparison with conventional **5-HT3 receptor antagonists**, and have a long duration of action.

Dwg.0/1

ABEQ US 5677326 A UPAB: 19971125
An indoline compound represented by the following formula (I), wherein

R1 represents the group of formula (a) or (b);

R2 represents a phenyl group which is substituted unsubstituted or an aromatic heterocyclic group, and R3 represents hydrogen, a halogen, or a lower alkyl group, hydroxyl group, lower alkoxy group, carbamoyl group or lower alkoxycarbonyl group;

or a physiologically acceptable salt or solvate of the compound.

Dwg.0/1

ABEQ EP 721949 B UPAB: 19980209
Indoline cpds. of formula (I) and their salts and solvates are new. R1 = indoline gp; R2 = phenyl or aromatic heterocyclic (both opt. substd.); R3 = H, halogen, lower alkyl, OH, lower alkoxy, carbamoyl or lower alkoxy

carbonyl.
USE - (I) are **5-HT3 receptor antagonists** useful for the prevention and **treatment** of vomiting or nausea induced by chemotherapy or radiation, **irritable bowel syndrome** and **diarrhoea**.
ADVANTAGE - (I) exhibit potent **5-HT3 receptor antagonist** activity in the intestinal tract, in comparison with conventional **5-HT3 receptor antagonists**, and have a long duration of action.
Dwg.0/1

L28 ANSWER 49 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1995-147378 [19] WPIDS
CR 1995-147379 [19]
AB WO 9509167 A UPAB: 19970313
Indoline derivs. of formula (I), their physiologically accepted salts and their solvates are new. R1 = gp. of formula (i) or (ii); R2 = phenyl or aromatic heterocyclic (both opt. substd.); R3 = H, halogen, lower alkyl, OH, lower alkoxy, carbamoyl or lower alkoxycarbonyl gp..
Also claimed is a **5-HT3 receptor antagonist** contg. (I).
USE - (I) are useful for prevention or **treatment** of vomiting or nausea induced by chemotherapy or radiation; **irritable bowel syndrome**, colitis, gastrointestinal motility disorders, **constipation** and **diarrhoea**; or migraine, headache, neuralgia, anxiety, psychiatric disorders, learning disorders, memory disorders, dementia, motion sickness, irregular pulse, post-operative nausea r vomiting, addiction to narcotics, alcohol or nicotine, or itching of the skin.
The dose is 0.01 mu g-1mg/kg per day administered orally, by injection or as a suppository.
ADVANTAGE - The indoline deriv. has a potent antagonism against 5-HT3 receptor in the intestinal tract in comparison with conventional **5-HT3 receptor antagonists** and has excellent persistence of activity.
Dwg.0/1

L28 ANSWER 50 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1994-333076 [41] WPIDS
AB WO 9422862 A UPAB: 19941206
Indolizine derivs. of formula (I) and their salts and solvates are new. In (I), R1 = opt. substd. phenyl; R2 = 5-R3-1H-imidazolyl-4-yl or 4-R3-1H-imidazol-5-yl; R3 = H, Me or Et.
Also claimed are intermediates of formula (II).
1 Cpd. (I) is claimed i.e. 2,3,8,9,10,11-hexahydro-9-((5-methyl-14-imidazol-4-yl)methyl)- 1-phenyl-8-oxo-1H-pyrido(4',3':4,5) pyrrolo(3,2,1-ij)quinoline (Ia).
USE/ADVANTAGE - (I) Are intestinal **5-HT3 receptor antagonists** useful in the **treatment** and prophylaxis of **irritable bowel syndrome**, **diarrhoea** and gastrointestinal dysfunction. (I) have potent and selective 5-HT3 antagonist activity and have reduced side effects compared to known cpds.

Dwg.0/0

L28 ANSWER 51 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
95052924 EMBASE Document No.: 1995052924. FK-1052. Agent for **irritable Bowel syndrome**. Prous J.; Mealy N.; Castaner J.. Prous Science Publishers, P.O. Box 540,08080 Barcelona, Spain. Drugs of the Future 19/12 (1075-1077) 1994. ISSN: 0377-8282. CODEN: DRFUD4. Pub. Country: Spain. Language: English.

L28 ANSWER 52 OF 69 CAPLUS COPYRIGHT 2000 ACS
1994:570454 Document No. 121:170454 **Constipation** evoked by 5-HT3-receptor antagonism: evidence for heterogeneous efficacy among different antagonists in guinea pigs. Sanger, G. J.; Wardle, K. A. (SmithKline Beecham Pharmaceuticals, Harlow/Essex, CM19 5AD, UK). J. Pharm. Pharmacol., 46(8), 666-70 (English) 1994. CODEN: JPPMAB. ISSN: 0022-3573.
AB The abilities of selective **5-HT3-receptor antagonists** to evoke **constipation** were examd. in conscious guinea-pigs and in prepns. of guinea-pig isolated colon. Compared with vehicle-**treated** guinea-pigs, acute doses of **granisetron** (0.1, 1 and 10 mg kg-1, i.p.) and **tropisetron** (10 mg kg-1, i.p., but not 1 and 0.1 mg kg-1, i.p.) significantly reduced the total no. of fecal pellets excreted during a 12-h observation period. By contrast, BRL 46470 (0.1-10 mg kg-1, i.p.) had no significant effect on the incidence of **defecation**. Mid-to-distal lengths of guinea-pig isolated colon spontaneously expelled fecal pellets. **Granisetron** (0.1 and 1 .mu.M) and **tropisetron** (1 .mu.M) reduced or prevented the rate at which they were spontaneously expelled. Morphine (0.1 .mu.M) and clonidine (10 nM) also slowed fecal pellet transit time. Naloxone (0.1 .mu.M) had no effects alone, but reversed the actions of **granisetron**, morphine and clonidine. BRL 46470 (1 .mu.m) had no significant effect on the transit of fecal pellets in guinea-pig isolated colon. In segments of guinea-pig isolated colon which did not contain fecal pellets, **granisetron, tropisetron** and BRL 46470 antagonized the ability of 5-HT to evoke cholinergically-mediated contractions of the longitudinal muscle. The resp. pA2 values and slopes of the Schild plots were 8.5, slope 1.06; 8.5, slope 0.91; and 7.9, slope 0.93. The authors expts. suggest that not all 5-HT2-receptor antagonists are the same. In particular, BRL 46470 does not prevent **defecation** or fecal pellet expulsion in guinea-pig colon, even though this compd. is an effective **5-HT3-receptor antagonist** in the same tissue. For the **5-HT3-receptor antagonists** which did cause **constipation**, the effects can be at least partly attributed to an indirect opioid-dependent action within the colonic enteric nervous system.

L28 ANSWER 53 OF 69 MEDLINE DUPLICATE 17
95047908 Document Number: 95047908. Serotonin (5-HT)3 receptors: antagonists and their pharmacological profiles. Miyata K; Honda K. (Institute for Drug

Discovery Research, Yamanouchi Pharmaceutical Co., Ltd., Tsukuba, Japan..) NIPPON YAKURIGAKU ZASSHI. FOLIA PHARMACOLOGICA JAPONICA, (1994 Sep) 104 (3) 143-52. Ref: 50. Journal code: F2X. ISSN: 0015-5691. Pub. country: Japan. Language: Japanese.

AB The pharmacology of 5-HT and the classification of 5-HT receptors have become increasingly complex. However, recent advances have produced a new nomenclature system for 5-HT receptors. 5-HT3 receptors are neuronal receptors coupled directly to cation channels. Recently, many selective **5-HT3-receptor antagonists** including **tropisetron**, **zacopride**, **ondansetron**, **granisetron**, zatosetron, nazasetron, YM060 and YM114 (KAE-393) have been developed. Many actions attributable to the 5-HT3-receptor have been described in both the peripheral and central nervous systems, and clinical trials are already showing the potential use of these **5-HT3 receptor antagonists** in a number of disorders of the gastrointestinal tract and central nervous system, such as nausea and vomiting induced by cancer chemotherapy, anxiety, depression, schizophrenia and migraine. In addition, endogenous 5-HT is suggested to be one of the substances that mediate stress-induced responses in gastrointestinal function, i.e., increase in fecal pellet output and **diarrhea**. Moreover, YM060, YM114 (KAE-393) and **granisetron** have been reported to inhibit restraint stress- and 5-HT-induced increases in fecal pellet output and **diarrhea** in rats and mice, indicating that endogenous 5-HT may mediate stress-induced changes in bowel function through the 5-HT3 receptor. Therefore, **5-HT3-receptor antagonists** are new **therapeutic** drugs for stress-induced gastrointestinal dysfunctions like **irritable bowel syndrome** (**IBS**).

L28 ANSWER 54 OF 69 MEDLINE DUPLICATE 18

94046965 Document Number: 94046965. **5-HT3 receptor antagonists**. 3. Quinoline derivatives which may be effective in the **therapy** of **irritable bowel syndrome**. Kishibayashi N; Miwa Y; Hayashi H; Ishii A; Ichikawa S; Nonaka H; Yokoyama T; Suzuki F. (Pharmaceutical Research Laboratories, Kyowa Hakko Kogyo Co., Ltd., Shizuoka-ken, Japan..) JOURNAL OF MEDICINAL CHEMISTRY, (1993 Oct 29) 36 (22) 3286-92. Journal code: J0F. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB A series of quinolinecarboxylic acid derivatives has been previously described as a new class of **5-HT3 receptor antagonists** due to deviation of a carbonyl moiety from the place of an aromatic ring in their minimum-energy conformations. These derivatives were evaluated in a wrap-restraint stress-induced **defecation** model in rats. Reference compounds, **ondansetron** (1), **granisetron** (2), and YM060 (4), potently inhibited a stress-induced increase in stools excreted from fed rats (ID50 = 0.27, 0.12, and 0.0052 mg/kg, po, respectively). However, quinoline derivatives exhibited different activities depending on structural class. 4-Hydroxyquinoline-3-carboxylic acid derivatives 5 and 6a possess high affinity for the 5-HT3 receptor (Ki = 6.1 and 1.5 nM, respectively) and exhibit potent activity in the Bezold-Jarisch (B-J) reflex test (ED50 = 0.0017 and 0.000 10 mg/kg, i.v., respectively), but they did not effectively inhibit the increase in fecal pellet output at the dose of 1 mg/kg, po. On the other hand, most of 1-substituted 2-oxoquinoline-4-carboxylates 10 showed less potent activity in the B-J reflex test than 1

or 2 but inhibited restraint stress-induced **defecation** more potently than 1 or 2. The ID50 value of endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl 1-isobutyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate 10e was 0.013 mg/kg, po. With respect to the selected compounds 6a and 10e, effects of 5-HT- and thyrotropin-releasing hormone (TRH)-induced **defecation**, castor oil-induced **diarrhea** and wrap-restraint stress-induced colonic propulsion in rats were examined. These **5-HT3 receptor antagonists** did not effectively inhibit castor oil-induced **diarrhea**, which has been reported not to be mediated via the 5-HT3 receptor. Although 10e showed 800-fold decreased potency compared with 4 in the B-J reflex test, 10e exhibited activity as potent as 4 in 5-HT- and TRH-induced **defecation** assays; 10e exhibited 7-fold increased potency compared with 4 in wrap-restraint stress-induced colonic propulsions. From these results, 10e appears to interact selectively with 5-HT3 receptors in the gastrointestinal system and might be effective in the **therapy** of **irritable bowel syndrome** (**IBS**).

L28 ANSWER 55 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

93206341 EMBASE Document No.: 1993206341. Prokinetic agents for lower gastrointestinal motility disorders. Longo W.E.; Vernava III A.M.. 3635 Vista Avenue at Grand Boulevard,St. Louis, MO 63110-0250, United States. Diseases of the Colon and Rectum 36/7 (696-708) 1993. ISSN: 0012-3706. CODEN: DICRAG. Pub. Country: United States. Language: English. Summary Language: English.

AB Prokinetic agents are currently being investigated as potential **therapies** for motility disorders of the lower gastrointestinal tract. Cholinergic agonists such as bethanechol are known to improve postoperative ileus but are limited because of side effects. Dopamine antagonists such as domperidone appear to have maximal prokinetic effect in the proximal gastrointestinal tract and are effective for such conditions as gastroparesis and gastroesophageal reflux, but they appear to have little physiologic effect in the colon or in colonic motility disorders. Naloxone, an opioid antagonist, appears to hold promise in patients with **irritable bowel syndrome**, small intestinal pseudo-obstruction, and **constipation**. Erythromycin exerts its prokinetic effect by acting as a motilin agonist; it has been used in the **treatment** of diabetic gastroparesis and appears to improve symptoms of colonic pseudo-obstruction and postoperative ileus. Metoclopramide, a combined cholinergic agonist and dopamine antagonist, is currently used exclusively for proximal motility dysfunction. Cisapride appears to hold the most promise for patients with colonic motility disorders. In patients with postoperative ileus, cisapride is associated with an increased return of bowel function compared with placebo. In patients with chronic **constipation**, cisapride increases stool frequency and decreases laxative abuse in both adults and children. Hopefully, as an understanding of gastrointestinal motility increases, effective prokinetic agents will be developed that will improve symptoms of patients with large bowel motility disorders and may also help to predict those patients who benefit from surgical management for **constipation**.

L28 ANSWER 56 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

93317902 EMBASE Document No.: 1993317902. Effect of a 5HT3-antagonist (**ondansetron**) on rectal sensitivity and compliance in health and the **irritable bowel syndrome**. Hammer J.; Phillips S.F.; Talley N.J.; Camilleri. Mayo Clinic, Gastroenterology Unit,Rochester, MN 55905, United States. Alimentary Pharmacology and Therapeutics 7/5 (543-551) 1993. ISSN: 0269-2813. CODEN: APTHEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB In some patients with the **irritable bowel syndrome**, rectal urgency and discomfort are major clinical problems and, under experimental conditions, these symptoms are perceived at lesser volumes of rectal distension than they are in asymptomatic controls. Further, a 5-hydroxytryptamine type-3 receptor antagonist increased the threshold for rectal discomfort in **irritable bowel syndrome**. Our aims were, (a) to measure rectal sensation during isobaric distensions of the rectum, and (b) to test the effect of another selective 5HT3-antagonist, **ondansetron** 0.15 mg/kg, on rectal sensitivity, colonic tone, rectal tone and manometric responses. Ten healthy volunteers and five patients with **diarrhoea** -predominant **irritable bowel syndrome** were studied. A multilumen barostat-manometric assembly was placed in the descending colon, and a second barostat balloon was positioned in the rectum. Tone in the wall of the colon and rectum was measured by the barostat balloon volume during a constant pressure clamp, while intraluminal pressures were recorded by manometry; perceived sensations were also recorded before and after the intravenous administration of **ondansetron** or placebo in blinded fashion. Rectal resistance to stretch was greater and rectal urgency was induced by lower distending pressures in **irritable bowel syndrome**, however, basl tone in the rectum was similar in health and **irritable bowel syndrome. Ondansetron** did not change rectal sensitivity (first sensation or urgency) or tone. Rectal distension did not alter tone in the descending colon or colonic manometry; **ondansetron** did not influence any index of colonic function. We conclude that in **diarrhoea**-predominant **irritable bowel syndrome** there is reduced rectal compliance and the rectum is abnormally sensitive to a pressure stimulus, but this is not altered by 5HT3-blockade with **ondansetron** at the dose used.

L28 ANSWER 57 OF 69 CAPLUS COPYRIGHT 2000 ACS
1994:124578 Document No. 120:124578 Pharmacological properties of KF18259, a novel **5-HT3-receptor antagonist**, in rats: inhibition of the distal colonic function. Kishibayashi, Nobuyuki; Ichikawa, Shunji; Yokoyama, Toshihide; Ishii, Akio; Karasawa, Akira (Dep. Pharmacol., Kyowa Hakko Kogyo Co., Ltd., Nagaizumi, 411, Japan). Jpn. J. Pharmacol., 63(4), 495-502 (English) 1993. CODEN: JJPAAZ. ISSN: 0021-5198.

AB The authors investigated the effects of KF18259 (endo-(8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-1-isobutyl-2-oxo-1,2-dihydro-4-quinolinecarboxylate hydrochloride), a novel **5-HT3-receptor antagonist**, in a variety of rat models, which are assumed to be mediated via 5-HT3 receptors, in comparison with those of YM060 ((R)-5-[(1-methyl-3-indolyl)carbonyl]-4,5,6,7-tetrahydro-1H-benzimidazole hydrochloride), **granisetron** and

ondansetron. KF18259 inhibited wrap-restraint stress-induced **defecation**. The doses of KF18259 to inhibit wrap-restraint stress-induced **defecation** were lower than those to inhibit the 5-HT-induced von Bezold-Jarisch reflex and the cisplatin-induced slowing of gastric emptying. In contrast, the doses of YM060, **granisetron** and **ondansetron** to inhibit these three responses were similar. Moreover, KF18259 inhibited the wrap-restraint stress-induced propulsive motility of the proximal and distal colon. The effect of KF18259 on the distal colon was as potent as that on **defecation** and was more potent than that on the proximal colon. These results indicate that KF18259 potently inhibits the distal colonic function. KF18259 may be a useful tool for the discrimination of the 5-HT3-receptors located on the distal colon and other tissues. The relation of these results to the **treatment** of **irritable bowel syndrome** is discussed.

L28 ANSWER 58 OF 69 MEDLINE DUPLICATE 19
93250225 Document Number: 93250225. Reduction of rectal sensitivity and post-prandial motility by **granisetron**, a **5 HT3 -receptor antagonist**, in patients with **irritable bowel syndrome**. Prior A; Read N W.
(Centre for Human Nutrition, Northern General Hospital, Sheffield, UK..)
ALIMENTARY PHARMACOLOGY AND THERAPEUTICS, (1993 Apr) 7 (2) 175-80.
Journal code: A5D. ISSN: 0269-2813. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB The effect of **granisetron**, a specific 5-hydroxytryptamine 3-receptor antagonist, on the anorectal responses to rectal distension and a 1000-calorie meal was assessed in 12 patients with **irritable bowel syndrome**. Each patient was studied on three occasions, receiving intravenously either 40 mcg/kg **granisetron**, 160 mcg/kg **granisetron** or normal saline. **Granisetron** caused a dose-dependent reduction in rectal sensitivity, manifested by an increase in the threshold volumes at which the sensations of gas, desire to **defecate**, urgency and discomfort were perceived. This reached significance for all sensations at the higher dose level ($P < 0.01$). No significant changes in anal pressures, rectal compliance or distension-induced motor activity occurred following drug administration. A dose-dependent reduction in post-prandial motility was observed following intravenous **granisetron** and this was highly significant at 160 mcg/kg ($P = 0.005$). These results suggest that the 5 hydroxytryptamine receptor antagonists may have a **therapeutic** role in patients with **irritable bowel syndrome**.

L28 ANSWER 59 OF 69 MEDLINE DUPLICATE 20
93330093 Document Number: 93330093. Nausea, abdominal pain and **diarrhoea** of uncertain cause responding to **ondansetron**.
Evans J E. MEDICAL JOURNAL OF AUSTRALIA, (1993 Jul 19) 159 (2) 125-7.
Journal code: M26. ISSN: 0025-729X. Pub. country: Australia. Language: English.
AB OBJECTIVE: To assess the value of **ondansetron** in a patient with intractable nausea, abdominal pain and **diarrhoea** unrelated to cancer chemotherapy or radiotherapy. CLINICAL FEATURES: A 33-year-old teacher presented with a three-and-a-half-year history of nausea,

abdominal pain and **diarrhoea**. She attended a consulting room in private practice for a second opinion as her symptoms had not responded to routine management of "**irritable bowel syndrome**". INTERVENTION: A prospective, non-placebo-controlled study was undertaken whereby she received **ondansetron** 8 mg three times daily for five days. Before ingestion of **ondansetron** it was planned that the efficacy of this new drug would be assessed by the clinical response and measured by the values obtained in a three-day faecal fat collection. OUTCOME: There was clinical benefit during the period of ingestion of **ondansetron**. In this time faecal weight and faecal fat excretion were reduced when compared with the results of similar collections (baseline study, and following the ingestion of pancreatic supplements) performed before the administration of **ondansetron**. CONCLUSION: The benefit obtained warrants further assessment. If confirmed, the results may suggest a role for **ondansetron** in the management of nausea and vomiting unrelated to cancer chemotherapy and radiotherapy.

L28 ANSWER 60 OF 69 MEDLINE DUPLICATE 21
93322999 Document Number: 93322999. Effect of FK1052, a potent 5-hydroxytryptamine3 and 5-hydroxytryptamine4 receptor dual antagonist, on colonic function in vivo. Kadowaki M; Nagakura Y; Tomoi M; Mori J; Kohsaka M. (Product Development Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, Japan..) JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1993 Jul) 266 (1) 74-80. Journal code: JP3. ISSN: 0022-3565. Pub. country: United States. Language: English.

AB 5-Hydroxytryptamine (5-HT) is an important neurotransmitter and hormone/paracrine agent mediating various enteric functions. Its precise physiological and pathophysiological role remains unclear. This study investigated the effects of 5-HT on colonic function and the effects of the newly developed 5-HT3 and 5-HT4 receptor antagonist, FK1052, on colonic responses to 5-HT or stress stimulus in vivo. In conscious rats, both 5-HT and 5-methoxytryptamine significantly increased fecal pellet output and accelerated colonic transit. In contrast, the effect of 2-methyl-5-HT was slight. Although **ondansetron** and **granisetron** slightly reduced 5-HT (1 mg/kg s.c.) stimulated colonic transit, FK1052 [(+)-8,9-dihydro-10-methyl-7-[(5-methyl-4-imidazolyl)methyl]pyrido- [1,2-a]-indole-6(7H)-one hydrochloride], at 0.1 mg/kg p.o., inhibited completely the increases in the colonic transit. Furthermore, FK1052, **ondansetron** and **granisetron** significantly depressed the increase in fecal pellet output caused by wrap-restraint stress, with ED50 values of 0.21, 3.0 and 1.1 mg/kg p.o., respectively. Intraperitoneal administration of 5-HT and 5-methoxytryptamine, but not 2-methyl-5-HT, produced a dose-related increase in the incidence of **diarrhea** in fasted mice. 5-HT (0.32 mg/kg i.p.)-induced **diarrhea** was also inhibited by FK1052, **ondansetron** and **granisetron**, with ED50 values of 0.09, 2.3 and 0.88 mg/kg p.o., respectively. These findings suggest that 5-HT3 and 5-HT4 receptors may have an important role in colonic function and FK1052 may have **therapeutic** potential in the **treatment** of gastrointestinal dysfunction such as **irritable bowel syndrome**.

L28 ANSWER 61 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-268596 [32] WPIDS
AB WO 9212149 A UPAB: 19931113
Azabicyclic and azatricyclic derivs. of formula X-A-Z (I) and their salts are new and have 5-HY3 antagonist activity. In (I), Z= 8-R-8-azabicyclo(3.2.1) octan-6-yl or 6-azatricyclo(4.3.1.04,9) decan-8-yl; X= phenyl or monocyclic 5- or 6-membered heteroaryl gp. both opt. fused to a satd. or unsatd. 5-7 membered carbocyclic or heterocyclic ring; A= a linking moiety; R= H or Me.

Also claimed are 6-amino-8-methyl-8-azabicyclo (3.2.1)octane and 8-amino-6-azatricyclo (4.3.1.04,9)decane.

A= e.g. CONH, COO, NHCONH, CONHCONH or a gp. (a). Two of G, H and O are O, S, N or C and the other is O, S or N; E= a bond or 1-5C alkylene opt. substd. by phenyl or OH.

2 Cpds. are specifically claimed, including (+-)-4-amino-5-chloro-2-methoxy -N-(8-methyl-8-aza-bicyclo (3.2.1)octan-6-yl)benzamide.

USE - (I) are **5-HT3 receptor antagonists** and are useful for the **treatment** of pain (including migraine, cluster headache, trigeminal neuralgia and visceral pain), emesis (esp. associated with cancer **therapy** including cisplatin, doxorubicin, cyclophosphamide and radiation **therapy**, surgery and migraine), CNS disorders (including anxiety, psychosis, cognitive disorders such as senile dementia and AAMI and drug dependence) and gastrointestinal disorders (including **irritable bowel syndrome** and **diarrhoea**). They may also be of use in the **treatment** of obesity, arrhythmia and myocardial instability. Unit doses are 0.05 to 1000 (0.5 to 500)mg and are administered pref. 1 to 3 times daily to give doses of 0.0001 to 50 (0.0002 to 25)mg/kg/day.

0/0

Dwg.0/0

ABEQ EP 566609 A UPAB: 19931207
Azabicyclic and azatricyclic derivs. of formula X-A-Z (I) and their salts are new and have 5-HY3 antagonist activity. In (I), Z= 8-R-8-azabicyclo(3.2.1) octan-6-yl or 6-azatricyclo(4.3.1.04,9) decan-8-yl; X= phenyl or monocyclic 5- or 6-membered heteroaryl gp. both opt. fused to a satd. or unsatd. 5-7 membered carbocyclic or heterocyclic ring; A= a linking moiety; R= H or Me.

Also claimed are 6-amino-8-methyl-8-azabicyclo (3.2.1)octane and 8-amino-6-azatricyclo (4.3.1.04,9)decane.

A= e.g. CONH, COO, NHCONH, CONHCONH or a gp. (a). Two of G, H and O are O, S, N or C and the other is O, S or N; E= a bond or 1-5C alkylene opt. substd. by phenyl or OH.

2 Cpds. are specifically claimed, including (+-)-4-amino-5-chloro-2-methoxy -N-(8-methyl-8-aza-bicyclo (3.2.1)octan-6-yl)benzamide.

USE - (I) are **5-HT3 receptor antagonists** and are useful for the **treatment** of pain (including migraine, cluster headache, trigeminal neuralgia and visceral pain), emesis (esp. associated with cancer **therapy** including cisplatin, doxorubicin, cyclophosphamide and radiation **therapy**, surgery and migraine), CNS disorders (including anxiety, psychosis, cognitive disorders such as senile dementia and AAMI and drug dependence) and gastrointestinal disorders (including **irritable bowel syndrome** and **diarrhoea**). They may also be of use in the **treatment** of obesity, arrhythmia and myocardial instability. Unit doses are 0.05 to 1000 (0.5 to 500)mg and are

administered pref. 1 to 3 times daily to give doses of 0.0001 to 50 (0.0002 to 25)mg/kg/day.

L28 ANSWER 62 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-250009 [30] WPIDS
AB WO 9211259 A UPAB: 19931006
Azabicyclic amides and esters of halogenated benzoic acids of formula (I) and their salts, having **5-HT3 receptor antagonists** activity, are new. In (I), R1 = H or 1-6C alkoxy; R2 and R3 = halo; L = O or NH; and Z = a di-azacyclic or azabicyclic side chain.

Specifically claimed are 5 Cpds. (I), e.g. endo-N-(8-methyl-8-azabicyclo (3.2.1)octan-3-yl-4 -amino -3,5-dichlorobenzamide.

USE/ADVANTAGE - Cpds. (I) are useful in the **treatment** and prophylaxis of pain, emesis,, CNS disorders and/or gastrointestinal disorders in mammals (claimed). For example, they may be used to **treat** migraine, cluster headache, trigeminal neuralgia and visceral pain; for preventing vomiting and nausea in cancer **therapy**, post-operative emesis and nausea in migraine; anxiety, psychosis, cognitive disorders and drug dependence; **irritable bowel syndrome** and **diarrhoea**. The cpds. are also of potential use in the **treatment** of obesity, arrhythmia, and/or disorders associated with myocardial instability. Cpds. (I) are pref. administered as oral compsns. at a dose of 0.0001-50, pref. 0.0002-25 mg/kg/day. A typical unit dose contains 0.05-1000 mg, e.g. 0.5-500 mg. No adverse toxic effects are indicated at these doses.
0/0
ABEQ EP 563087 A UPAB: 19931129
Azabicyclic amides and esters of halogenated benzoic acids of formula (I) and their salts, having **5-HT3 receptor antagonists** activity, are new. In (I), R1 = H or 1-6C alkoxy; R2 and R3 = halo; L = O or NH; and Z = a di-azacyclic or azabicyclic side chain.

Specifically claimed are 5 Cpds. (I), e.g. endo-N-(8-methyl-8-azabicyclo (3.2.1)octan-3-yl-4 -amino -3,5-dichlorobenzamide.

USE/ADVANTAGE - Cpds. (I) are useful in the **treatment** and prophylaxis of pain, emesis,, CNS disorders and/or gastrointestinal disorders in mammals (claimed). e.g., they may be used to **treat** migraine, cluster headache, trigeminal neuralgia and visceral pain; for preventing vomiting and nausea in cancer **therapy**, post-operative emesis and nausea in migraine; anxiety, psychosis, cognitive disorders and drug dependence; **irritable bowel syndrome** and **diarrhoea**. The cpds. are also of potential use in the **treatment** of obesity, arrhythmia, and/or disorders associated with myocardial instability. Cpds. (I) are pref. administered as oral compsns. at a dose of 0.0001-50, pref. 0.0002-25 mg/kg/day. A typical unit dose contains 0.05-1000 mg, e.g. 0.5-500 mg. No adverse toxic effects are indicated at these doses.

L28 ANSWER 63 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-234572 [28] WPIDS
AB WO 9210494 A UPAB: 19931006
Benzo-dioxan and -dioxole derivs. of formula (I) and their salts having **5-HT3 receptor antagonist** activity are new, R1 = H, halo, NO2, NH2, 1-6C alkyl or 1-6C alkoxy; R2 = halogen,

1-6C alkyl or 1-6C alkoxy; A = 1-3C polymethylene (opt. substd. by 1 or 2 1-6C alkyl gps.), L = O or pref. NH; and Z = di-azacyclic or azabicyclic side chain. More specifically Z = granatane, thia-grantane, quinuclidine, isoquinuclidine, isogranatane, oxa/thia-isogranatane or isotropane or esp.
tropane, oxagranatane or azagranatane.
USE - (I) are useful for the **treatment** of pain (esp. migraine, cluster headache, trigeminal neuralgia and visceral pain), emesis (esp. associated with cancer **therapy**, post-operative emesis and nausea associated with migraine), CNS disorders (esp. anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory (impairment and drug dependence) and gastrointestinal disorders (esp. **irritable bowel syndrome** and **diarrhoea**). They may also be of use in the **treatment** of obesity, arrhythmia and myocardial instability. Unit doses are 0.05 to 1000 mg, pref. 0.5 mg, which are administered 1 to 3 times daily giving daily doses of 0.0001-50 pref. 0.0002 - 25 mg/kg/day.
0/0

ABEQ EP 561910 A UPAB: 19931123
Benzo-dioxan and -dioxole derivs. of formula (I) and their salts having **5-HT3 receptor antagonist** activity
are new, R1 = H, halo, NO2, NH2, 1-6C alkyl or 1-6C alkoxy; R2 = halogen, 1-6C alkyl or 1-6C alkoxy; A = 1-3C polymethylene (opt. substd. by 1 or 2 1-6C alkyl gps.), L = O or pref. NH; and Z = di-azacyclic or azabicyclic side chain. More specifically Z = granatane, thia-grantane, quinuclidine, isoquinuclidine, isogranatane, oxa/thia-isogranatane or isotropane or esp.
tropane, oxagranatane or azagranatane.
USE - (I) are useful for the **treatment** of pain (esp. migraine, cluster headache, trigeminal neuralgia and visceral pain), emesis (esp. associated with cancer **therapy**, post-operative emesis and nausea associated with migraine), CNS disorders etc.
Dwg.0/0

L28 ANSWER 64 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1992-132068 [16] WPIDS
AB WO 9205174 A UPAB: 19931006
3,9-Diazabicyclo (3.3.1) nonan-7-yl derivs. of formula (I) or their salts having **5-HT3 receptor antagonist**
activity, are new. X = phenyl or monocyclic 5- or 6-membered heteroaryl both opt. fused to an opt. unsatd. 5-7 membered carbocyclic or heterocyclic ring; A = a linking moiety; Z = 1-6C alkyl, 3-8C cycloalkyl, 3-8C cycloaklyl (1-4C)alkyl, phenyl, naphthyl, phenyl(1-4C)alkyl or naphthyl(1-4C) alkyl, where the phenyl or naphthyl moiety is opt. substd. by 1 or more of halo, 1-6C alkoxy or 1-6C alkyl; R = H or Me.
20 cpds. (I) e.g. endo-4-amino-5-chloro-2-methoxy-N-(3-benzyl-9-methyl-3,9-diazabicyclo(3.3.1)nonan-7-yl) benzamide; endo-N-3,3-dimethylindolin-1-yl- (3-isopropyl-9- methyl-3,9-diazabicyclo(3.3.1) nonan-7-yl carboxamide; and endo-N-1-methyl-3-indazolyl-(3-butyl-9-methyl -3,9-diazabicyclo (3.3.1)nonan-7-yl) carboxamide are specifically claimed.
USE - (I) may be used to **treat**/prevent pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headaches, trigeminal neuralgia and visceral pain; emesis includes preventing vomiting and nausea associated with cancer **therapy**, post-operative emesis, and nausea associated with migraine, CNS disorders

include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI) and drug dependence; gastrointestinal disorders include **irritable bowel syndrome** and **diarrhoea**. Some (I) may also have gastric protionetic activity. Admin. is in unit doses, 1-3 times a day, of 0.0001-50 (pref. 0.0002-25) mg/kg. (0/0)
0/0

ABEQ EP 550550 A UPAB: 19931116
3,9-Diazabicyclo(3.3.1) nonan-7-yl derivs. of formula (I) or their salts having **5-HT3 receptor antagonist** activity, are new, where X = phenyl or monocyclic 5- or 6-membered heteroaryl both opt. fused to an opt. unsatd. 5-7 membered carbocyclic or heterocyclic ring; A = a linking moiety; Z = 1-6C alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl (1-4C) alkyl, phenyl, naphthyl, phenyl(1-4C)alkyl or naphthyl(1-4C)alkyl, where the phenyl or naphthyl noiety is opt. substd. by 1 or more of halo, 1-6C alkoxy or 1-6C alkyl; R = H or Me.

20 Cpds. (I) e.g. endo-4-amino-5-chloro-2-methoxy-N-(3-benzyl-9 -methyl-3,9)- diazabicyclo(3.3.1) nonan-7-yl) benzamide; endo-N-3,3 -dimethylindolin-1-yl- (3-isopropyl -9-methyl-3,9- diazabicyclo(3.3.1) nonan-7-yl carboxamide; and endo-N-1-methyl- 3-indazolyl -(3-butyl-9-methyl -3,9-diazabicyclo(3.3.1)nonan-7-yl) carboxamide are specifically claimed.

USE - (I) may be used to **treat**/prevent pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headaches, trigeminal neuralgia and visceral pain; emesis includes preventing vomiting and nausea associated with cancer therepy, post-operative emesis and nausea associated with migraine, CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI) and drug dependence; gastrointestinal disorders include **irritable bowel syndrome** and **diarrhoea**. Some (I) may also have gastric protionetic activity. Admin. is in unit doses, 1-3 times a day, of 0.0001-50 (pref. 0.0002-25) mg/kg.

L28 ANSWER 65 OF 69 MEDLINE DUPLICATE 22
93061373 Document Number: 93061373. Selective 5-hydroxytryptamine type 3 receptor antagonism with **ondansetron** as **treatment** for **diarrhea**-predominant **irritable bowel syndrome**: a pilot study [see comments]. Steadman C J; Talley N J; Phillips S F; Zinsmeister A R. (Gastroenterology Research Unit, Mayo Clinic, Rochester, MN 55905..) MAYO CLINIC PROCEEDINGS, (1992 Aug) 67 (8)
732-8. Journal code: LLY. ISSN: 0025-6196. Pub. country: United States. Language: English.

AB Serotoninergic innervation may contribute to the control of colonic motility and to visceral sensation from the large bowel. Indeed, **ondansetron** hydrochloride, a selective 5-hydroxytryptamine type 3 receptor antagonist, has been shown to slow colonic transit in healthy volunteers. Thus, we wished to determine whether 5-hydroxytryptamine type 3 receptor blockade slows colonic and small bowel transit in patients with **diarrhea**-predominant **irritable bowel syndrome** (**IBS**) and whether symptoms would be ameliorated with drug **therapy**. Of 14 patients with well-established **IBS** who entered a randomized, double-blind, placebo-controlled crossover pilot trial of 4 weeks of **treatment** with

ondansetron, 16 mg three times daily, 11 completed the study. A minimal "washout period" of 4 weeks (median, 7 weeks) separated the two phases of the trial because patients were required to have similar symptoms before both periods of the study. Colonic transit tended to be longer during drug **therapy** than during the placebo trial, but this difference was not significant. Small intestinal transit and orocecal transit were unchanged by the drug. The integrated and peak postprandial increases in neurotensin, peptide YY, and human pancreatic polypeptide in serum were not significantly different in the drug and placebo periods. After **treatment** with **ondansetron**, stool consistency improved significantly; however, stool frequency, stool weight, abdominal pain, and the symptom criteria for **IBS** were not significantly altered by the drug. The results of this pilot study suggest that the motor effects expected with 5-hydroxytryptamine type 3 receptor blockade (namely, slowed colonic transit) may be diminished in some patients with **IBS**. The subjective improvement in stool consistency may reflect changes in the perception of **defecation**.(ABSTRACT TRUNCATED AT 250 WORDS)

L28 ANSWER 66 OF 69 MEDLINE

92132476 Document Number: 92132476. Closing remarks. **Ondansetron**: effects on gastrointestinal motility. Lamers C B. (Dept. of Gastroenterology, University Hospital, Leiden, The Netherlands..) SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT, (1991) 188 124-6. Ref: 22. Journal code: UCT. ISSN: 0085-5928. Pub. country: Norway. Language: English.

AB **Ondansetron** (GR 38032F), a 5-hydroxytryptamine-3 (**5-HT3**) **receptor antagonist**, is a highly effective and safe drug for the prophylaxis and **treatment** of emesis induced by various chemotherapy regimens in cancer patients. Recent studies have shown that **ondansetron** is also effective in post-anaesthesia and radiation-induced nausea and vomiting. When compared with high-dose metoclopramide, **ondansetron** appeared to be superior. Furthermore, **ondansetron** has been shown to improve stool consistency and to reduce stool frequency in patients with **diarrhoea**-predominant **irritable bowel syndrome**.

L28 ANSWER 67 OF 69 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

92019086 EMBASE Document No.: 1992019086. **Ondansetron**: Effects on gastrointestinal motility. Lamers C.B.H.W.. Dept. of Gastroenterology, Building 1, C4-PO15, University Hospital, PO Box 9600,2300 RC Leiden, Netherlands. Scandinavian Journal of Gastroenterology, Supplement 26/188 (124-126) 1991.
ISSN: 0085-5928. CODEN: SJGSB8. Pub. Country: Norway. Language: English. Summary Language: English.

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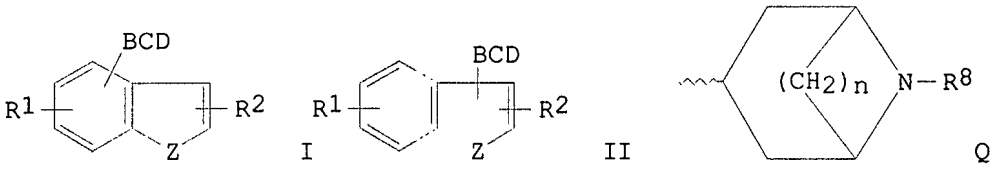
superior. Furthermore, **ondansetron** has been shown to improve stool consistency and to reduce stool frequency in patients with **diarrhoea**-predominant **irritable bowel syndrome**.

L28 ANSWER 68 OF 69 CAPLUS COPYRIGHT 2000 ACS
1990:565432 Document No. 113:165432 Azabicyclo derivatives of (hetero)cyclic
esters and amides for **treatment** of serotonin-induced gastrointestinal disorders, and pharmaceutical compositions containing them. Buchheit, Karl Heinz (Sandoz A.-G., Switz.). U.S. US 4910193 A 19900320, 10 pp. Cont. of U.S. Ser. No. 809,541, abandoned. (English). CODEN: USXXAM. APPLICATION: US 1987-90986 19870828. PRIORITY: US 1985-809541 19851216.

GI



AB The title compds., e.g. I or II [Z = CH2, O, S, NR3; R1, R2 = H, halo, C1-4 alkyl, C1-4 alkoxy, OH, amino, SH, etc.; R3 = H, C1-4 alkyl, C3-5 alkenyl, Ph, PhCH2; B = C(O), SO2; C = O, NH; D = Q (n = 2-4; R8 = C1-7 alkyl, C3-5 alkenyl, PhCH2)], or their pharmaceutically acceptable acid addn. or quaternary ammonium salts, are provided for **treatment** of a serotonin-induced gastrointestinal disturbance (gastritis, peptic ulcer, spastic colon, Crohn's disease, etc.). The compds. of the invention preferentially block the low-affinity 5-HT receptors, thereby inhibiting 5-HT-induced contraction, at .apprx.10-7-10-9M. Thus, indole-3-carboxylic acid endo-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester (III) produced a maximal response at 10-8M in facilitating field stimulation-induced contractions in muscle strips from different parts of the guinea pig stomach; III was 100-fold more active than metoclopramide. III inhibited 5-hydroxytryptophan-induced gastrointestinal motility with an i.p. ED50 = 70 .mu.g/kg. A tablet formulation for oral administration contained III 16.9, hydroxypropylcellulose 1.2, corn starch 12.0, lactose 92.8, silica 0.6, and Mg stearate 1.5 mg.

L28 ANSWER 69 OF 69 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1990-083767 [12] WPIDS
AB AU 8939103 A UPAB: 19931202
(A) Indazole-3 carboxylic acid derivs. of formula (I) and their acid-addn.
and quat. ammonium salts are new: Y = NH or O; R1 and R2 = H, opt. substd.
alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, opt. substd. aralkyl, alkoxycarbonyl, opt. substd. aralkoxycarbonyl or acyl, or R1+R2 =
alkylene; R3 = H, alkyl or phenyl; R4 = H, opt. substd. alkyl, cycloalkyl,
alkenyl, cycloalkenyl, alkynyl, opt. substd. aralkyl, alkoxycarbonyl or

opt. substd. aralkoxycarbonyl; R5 = H, halogen, alkyl, alkoxy, OH, CF3, NO2, NH2 or acylamino; m and p = 1-4; n = 1-3.

(B) Intermediates of formula (IIIa) are also new: R'1 and R'2 are as defined for R1 and R2, but not both benzyl; Z2 = NR6R7 or OR6; R6 = H, alkoxycarbonyl, opt. substd. aralkoxycarbonyl or acyl; R7 = H, alkoxycarbonyl, opt. substd. aralkoxycarbonyl, acyl, alkylsulphonyl, opt. substd. arylsulphonyl or trityl; or NR6R7 = phthalimido.

USE - (I) are selective serotonin 3 (**5-HT3**) **receptor antagonists** useful for **treating** anorexia, nausea, vomiting and abdominal discomfort associated with gastritis, peptic ulcers, gastric neurosis and gastroptosis; oesophagal and bile duct disorders; urinary tract disorders; **diarrhoea** and **constipation** associated with **irritable bowel syndrome** or carcinoid syndrome; nausea and vomiting associated with cancer **therapy** or motion sickness; cluster headaches, migraine and trigeminal neuralgia; psychotic disorders; cardiac disorders; obesity; pulmonary embolism; rhinitis and serotonin-induced rhinopathy; somnolence; pain; and drug intoxication.

Dwg.0/0

ABEQ US 5017573 A UPAB: 19930928

An indazole-3-carboxylic acid cpd. of formula (I) or its physiologically acceptable acid addn. salt or quat. ammonium salt is claimed. In (I) Y is -NH- or -O-; R1 and R2 are each H; 1-6C alkyl opt. substd. by 3-8C cycloalkyl, 5-8C cycloalkenyl, 1-6C alkoxy, hydroxy etc.; 3-8C cycloalkyl, 2-6C alkenyl; 5-8C cycloalkenyl; 2-6C alkynyl; phenyl opt. substd. by halogen, 1-6C alkyl, CF3 etc.; 2-6C alkoxycarbonyl; phenyl-1-6C-alkoxycarbonyl (with opt. substd. phenyl); 2-6C alkanoyl; opt. substd. benzoyl; or R1 and R2 together form 1-6C alkylen; R3 is H, 1-6C alkyl or phenyl; R4 is H, 1-6C alkyl; substd.-1-6C alkyl; 3-8C cycloalkyl; 2-6C alkenyl; 5-8C cycloalkenyl, 2-6C alkynyl, opt. substd. phenyl, 2-6C alkoxycarbonyl, phenyl 1-6C-alkoxycarbonyl, 2-6C alkanoyl or opt. substd. benzoyl; R5 is H, halogen, 1-6C alkyl, 1-6C alkoxy, hydroxy, CF3, nitro, amino, 2-6C alkanoylamino or benzoylamino; m is 1 or 2; n is 2 or 3 and p is 1, 2 or 3.

N-(1-(3-methylbenzyl) -4-methylhexahydro -1H-1,4-diazepin-6-yl) -1H-indazole-3-carboxamide is one of the cpds. specifically claimed.

USE - Cpd. is useful as a potent and selective antagonist of serotonin 3(5-HT3) receptor.

ABEQ US 5166341 A UPAB: 19930928

6-Amino-1,4-hexahydro-1H-diazepine intermediates of formula (III) are new.

In (III), R1 and R2 are each H, 1-6C alkyl, opt. substd. 3-8C cycloalkyl, 2-6C alkenyl and alkynyl, 5-8C cycloalkenyl, Ph (1-6C) alkyl, an -alkoxycarbonyl, opt. substd. 2-6C alkanoyl, or benzyl, opt. substd. or together are 1-6C alkylene; R3 is H, 1-6C alkyl or Ph; Z2 is NR6R7 with R6 is H, and R7 is H, 2-6C alkoxycarbonyl, Ph(1-6C)alkoxycarbonyl, opt. substd. 2-6C alkanoyl, benzoyl opt. substd. 1-6C alkylsulphinyl, or Ph sulphinyl, opt. substd. or trityl; or R6 and R7 together with the N are phthalimide; m is 1 or 2; n is 1; with provisos.

A typical cpd. is 6-acetylamino-1-benzyl- 4-methylhexahydro-1H-1,4-diazepine.

USE - (III) are intermediates to indazolo-3-carbocyclic acid derivs. of formula (I), where R4 is H, 1-6C alkyl, opt. substd. alkenyl, alkynyl,

or cycloalkenyl, etc, and R5 is H, halo, 1-6C alkyl or alkoxy, OH, CF3, etc. (I) are potent selective serotonin 3 (5HT3)receptor antagonists used to **treat** anorexia, nausea, vomiting and chronic gastritis esp. after anti-cancer drugs and for motion sickness.

Dosage is, e.g., 0.0001-20 (0.001-5) mg/kg/day.

0/0

ABEQ JP 05092959 A UPAB: 19931113

Cyclic diamine cpds.(I) or their physiologically tolerable acid addition salts or quat. ammonium salts are new. In (I), R1 and R2 = H, lower alkyl, cycloalkyl, lower alkenyl, cycloalkenyl, lower alkinyl, aryl (lower) alkyl, lower alkoxycarbonyl, aryl (lower) alkoxyloxycarbonyl or acyl or R1 and R2 in combination from lower alkylene; R3 = H, lower alkyl or phenyl; A = gp. of formula (a), (b) or (c). R4 = H, lower alkyl, cycloalkyl, cycloalkenyl, lower alkenyl, lower alkinyl, aryl (lower) alkyl, O or lower alkyl interrupted with carbonyl, lower alkoxycarbonyl, aryl (lower) alkyloxycarbonyl or aryl; R5 = H, halogen, lower alkyl, hydroxy, lower alkoxy, trifluoromethyl, nitro, amino, mono- or di-substituted amino, acylamino or cyano; R7 = H, hydroxy, acyloxy, lower alkoxy or alkoxy interrupted with O; Y = -R8- or single bond; R8 = H or lower alkyl or R8 in combination R7 forms lower alkylene; Het = monocyclic heteroaryl or dicyclic heteroaryl except 1H-indazolyl; p = 1, 2, 3 or 4; q = 0, 1 or 2; s = 1, 2 or 3; B = -CXNR6(CH2)y-, -COO(CH2)y-, -NR6CX(CH2)y- or -NR6(CH2)y-; R6 = H, lower alkyl or acyl; X = O or S; y = 0, 1, 2 or 3; m = 1, 2, 3 or 4; n = 1, 2 or 3. But except (i) A = (a), q = 0 and B = -CONH; (ii) A = (b), Y = -NR8- and B = -NR6CX(CH2)y- or -NR6(CH2)y-.

USE - New cpds. (I) have strong and selective serotonin 3 (5HT3) acceptor antagonism and they are useful as pharmaceuticals, antagonists to serotonin 3 (5 HT3) acceptor, remedy and preventive for various nausea or emesis. Cpds. (II) are useful as intermediates for the prodn. of cpds. (I).

Dwg.0/0

ABEQ EP 358903 A UPAB: 19931116

(A) Indazole-3 carboxylic acid derivs. of formula (I) and their acid-addn. and quat. ammonium salts are new: Y = NH or O; R1 and R2 = H, opt. substd. alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, opt. substd. aralkyl, alkoxycarbonyl, opt. substd. aralkoxycarbonyl or acyl, or R1+R2 = alkylene; R3 = H, alkyl or phenyl; R4 = H, opt. substd. alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, opt. substd. aralkyl, alkoxycarbonyl or opt. substd. aralkoxycarbonyl; R5 = H, halogen, alkyl, alkoxy, OH, CF3, NO2, NH2 or acylamino; m and p = 1-4; n = 1-3.

(B) Intermediates of formula (IIIa) are also new: R'1 and R'2 are as defined for R1 and R2, but not both benzyl; Z2 = NR6R7 or OR6; R6 = H, alkoxycarbonyl, opt. substd. aralkoxycarbonyl or acyl; R7 = H, alkoxycarbonyl, opt. substd. aralkoxycarbonyl, acyl, alkylsulphonyl, opt. substd. arylsulphonyl or trityl; or NR6R7 = phthalimido.

USE - (I) are selective serotonin 3 (**5-HT3**) **receptor antagonists** useful for **treating** anorexia, nausea, vomiting and abdominal discomfort associated with gastritis, peptic ulcers, gastric neurosis and gastroptosis; oesophagal

and bile duct disorders; urinary tract disorders; **diarrhoea** and **constipation** associated with **irritable bowel syndrome** or carcinoid syndrome; nausea and vomiting associated with cancer **therapy** or motion sickness; cluster headaches, migraine and trigeminal neuralgia; psychotic disorders; cardiac disorders; obesity; pulmonary embolism; rhinitis and serotonin-induced rhinopathy; somnolence; pain; and drug intoxication.

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'IN' IS NOT A VALID FIELD CODE
L29          61 FILE MEDLINE
L30          58 FILE CAPLUS
L31          90 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L32          64 FILE EMBASE
L33           3 FILE WPIDS

TOTAL FOR ALL FILES
L34         276 MANGEL A?/AU,IN


'IN' IS NOT A VALID FIELD CODE
L35           0 FILE MEDLINE
L36           0 FILE CAPLUS
L37           0 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L38           0 FILE EMBASE
L39           0 FILE WPIDS

TOTAL FOR ALL FILES
L40           0 NORTHOUTT A?/AU,IN

=> dis his


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RAMO

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L3         2176 FILE CAPLUS
L4         3090 FILE BIOSIS
L5         5918 FILE EMBASE
L6           76 FILE WPIDS
     TOTAL FOR ALL FILES
L7        14286 S (ALOSETRON OR GRANISETRON OR AZASETRON OR TROPISETRON OR
RAMO
L8           256 FILE MEDLINE
L9           117 FILE CAPLUS
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L10          242 FILE MEDLINE
L11          117 FILE CAPLUS
L12          199 FILE BIOSIS
L13          719 FILE EMBASE
L14           17 FILE WPIDS
     TOTAL FOR ALL FILES
L15         1294 S (L7 OR 5 HT3 RECEPTOR ANTAGONIST) AND (C6.405.469.237/CT OR
C
L16           25 FILE MEDLINE
L17           23 FILE CAPLUS
L18           24 FILE BIOSIS
L19           50 FILE EMBASE
L20           11 FILE WPIDS
     TOTAL FOR ALL FILES
L21          133 S L15 AND (IBS OR IRRITABLE BOWEL SYNDROME OR
C6.405.469.158.27
L22           21 FILE MEDLINE
L23           17 FILE CAPLUS
L24           14 FILE BIOSIS
L25           47 FILE EMBASE
L26           11 FILE WPIDS
     TOTAL FOR ALL FILES
L27          110 S L21 AND (THERAP? OR TREAT?)
L28           69 DUP REM L27 (41 DUPLICATES REMOVED)
L29           61 FILE MEDLINE
L30           58 FILE CAPLUS
L31           90 FILE BIOSIS
L32           64 FILE EMBASE
L33            3 FILE WPIDS
     TOTAL FOR ALL FILES
L34          276 S MANGEL A?/AU,IN
L35            0 FILE MEDLINE
L36            0 FILE CAPLUS
L37            0 FILE BIOSIS
L38            0 FILE EMBASE
L39            0 FILE WPIDS
     TOTAL FOR ALL FILES
L40            0 S NORTHOUTT A?/AU,IN

=> s l34 and l21

L41            3 FILE MEDLINE
L42            2 FILE CAPLUS
L43            3 FILE BIOSIS
L44            4 FILE EMBASE
L45            1 FILE WPIDS

TOTAL FOR ALL FILES
L46           13 L34 AND L21

=> s l46 not l27

L47            0 FILE MEDLINE
L48            0 FILE CAPLUS
L49            1 FILE BIOSIS
L50            0 FILE EMBASE
```